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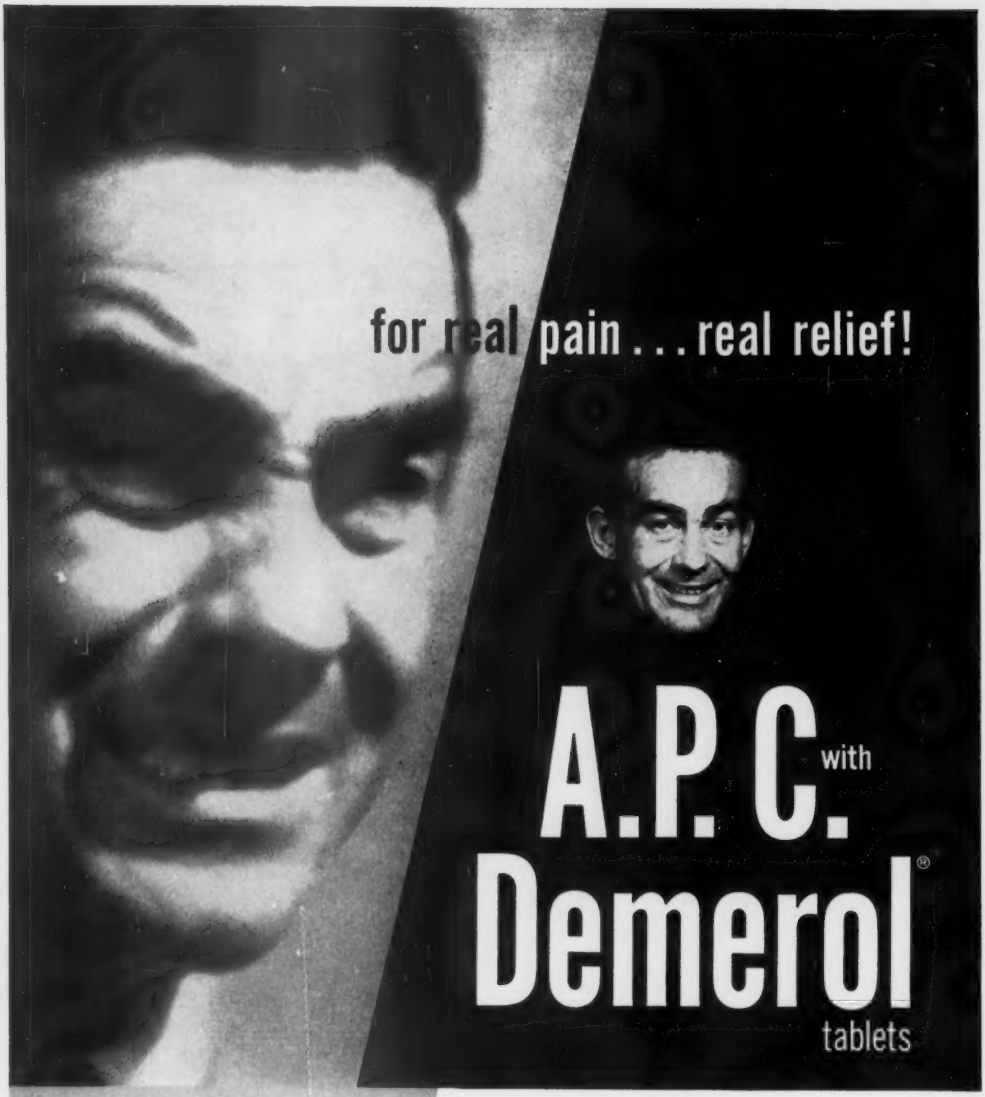

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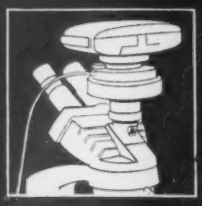

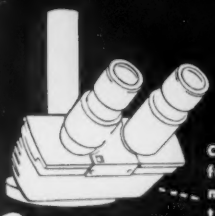

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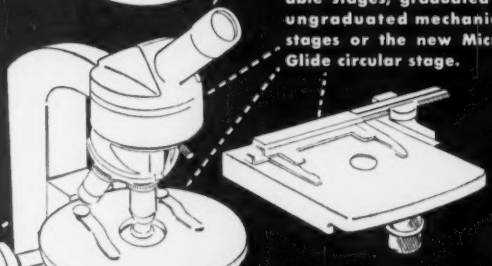

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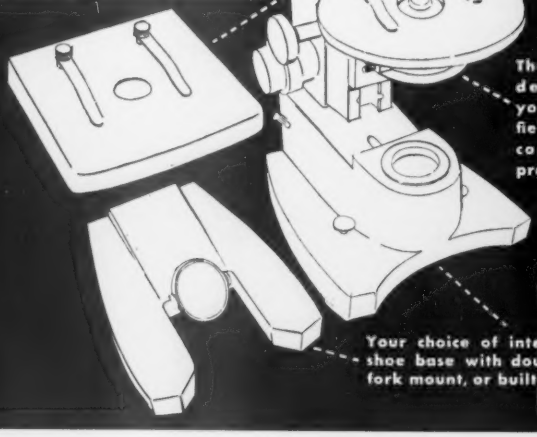

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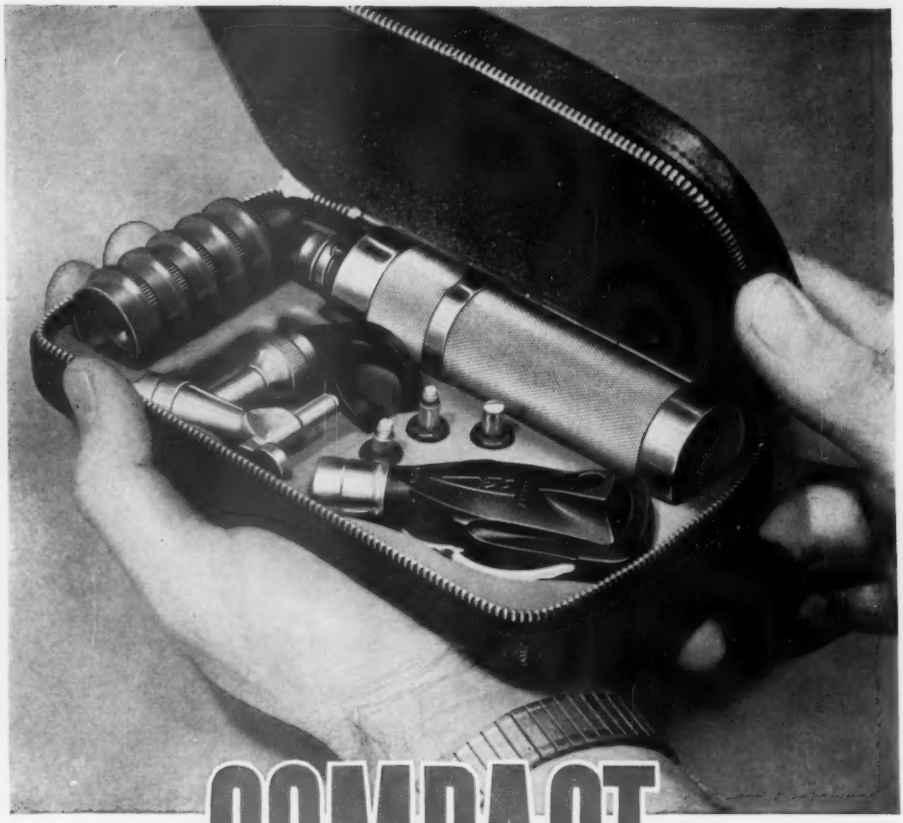

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MEDICINE IN THE NINETEENTH CENTURY—WITH SPECIAL REFERENCE TO THE UNITED STATES†

In 1901, in order to ring out the old century and ring in the new, an enterprising New York publisher issued a survey of nearly six hundred pages, entitled *The progress of the century.* No name appears on the title-page as that of editor and there is no preface, no introduction, and no indication of the scope or purpose of the volume. Beginning with an essay on evolution by Alfred Russel Wallace, it concludes with an essay on free thought by Goldwin Smith, and may be said to encompass, in the fifteen contributions which lie between, most of the broad areas of thought and activity which lie outside the spheres of politics and economics. William Osler of Baltimore contributed a chapter on medicine and W. W. Keen of Philadelphia, a chapter on surgery.

We have already heard in the course of this symposium of some of the wonderful changes which have taken place during the last fifty, the last twenty and even the last ten years, of the great range of current activity in every branch of medicine, and of the marvels which may be in store for us in the future. Sixty years ago, however, it already appeared that enormous strides had been taken, and that darkness had been pushed back a long way at all the frontiers of light.

> For countless generations [wrote Osler] the prophets and kings of humanity have desired to see the things which men have seen, and to hear the things which men have heard in the course of the wonderful nineteenth century. To the call of the watchers on the towers of progress there had been the one sad answer—the people sit in darkness and in the shadow of death. Politically, socially, and morally the race had improved, but for the unit, for the individual, there was little hope. Cold philosophy shed a glimmer of light on his path, religion in its various guises illumined his sad heart, but neither availed to lift the curse of suffering from the sin-begotten son of Adam. In the fulness of time, long expected, long delayed, at last Science emptied upon him from the horn of Amalthea blessings which cannot be enumerated, blessings which have made the century forever memorable; and which have followed each other with a rapidity so bewildering that we

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know not what next to expect. To us in the medical profession, who deal with this unit, and measure progress by the law of the greatest happiness to the greatest number, to us whose work is with the sick and suffering, the great boon of this wonderful century, with which no other can be compared, is the fact that the leaves of the tree of Science have been for the healing of the nations.

Thus far Osler. It was not to be expected that in a book which was meant to celebrate the progress of one hundred years—yes, and of one hundred years which truly marked a great abyss between the old and the new—much space should be given to a catalogue of failures and frustrations. Several of the authors, and Osler among the rest, did indeed suggest that many large tracts of unknown country remained to be explored; but there is no suggestion in the section on medicine that the limitations of the pharmacopoeia, to take one example of an undeveloped terrain, seemed to Osler to constitute a severe restriction on useful effort in medicine. He exulted not only in what he and his colleagues knew about human biology, but also in what they were able then to do for the relief of human suffering, and for the prevention, even for the cure, of disease. If, however, the mood of 1901 was on the whole a mood of exultation, the glorious nineteenth century had had other moods as well. As Iago Galdston has pointed out, "in the autobiographical writings of many of the physicians of that period there is to be found an undertone of despair; a depressing awareness of their powerlessness; a disconcerting sense of their blind gropings and the futility of much that they did only because something had to be done, and they knew of nothing better."

During a substantial part of the century, certainly during its first half, the survival of the old regime is at least as apparent, looking back from 1960, as the innovation which was opening doors to a new era. "One of the astonishing features in medical history," writes Walter Pagel, "is the tenacity with which humoral pathology—an ancient Greek conception—maintained its ruling position far into the eighteenth and even the first half of the nineteenth centuries." This Dr. Pagel proceeds to illustrate as a lingering anachronism in the history of tuberculosis. Gabriel Andral, for example, who revived humoral pathology in general, emphasized the inflammatory, purulent, and "secretory" nature of tubercular changes and even "tried to reverse the advance which Laennec had achieved by stating that haemoptysis was one of the common causes of phthisis"—this in opposition to the long-neglected seventeenth-century discovery of Franciscus Sylvius that haemorrhage is a secondary event in lung cavitation, and to much good work in the interval between Sylvius and Laennec. The Greeks had reclaimed their dominion.

It was therefore one of the major tasks of nineteenth-century scientists, certainly not least in the field of medicine, to clear ground, to get rid of lingering anachronisms, to consign old Galen to the flames (as he had been consigned so often before), and to prepare the way for new things. This negative task carried with it a certain exhilaration, too, so that clearing out the pharmacopoeia was not necessarily a depressing job. A good start had been made in the eighteenth century. When the nineteenth century was over, an amazing number of bottles and boxes remained in the dispensary. But whereas the short list of really useful drugs at the doctor's disposal has been mentioned here by another speaker as one of the grave shortcomings of medicine only twenty years ago, Osler, as is well known, paraded a short list of specifics a century back as a sign of medicine's enlightenment. Like Oliver Wendell Holmes before him, he rejoiced at the wholesale rejection of much of the long tradition of drug therapy. It is needless, perhaps, to add that polypharmacy, like Galen, is buried with suitable ceremonies once in every generation but unaccountably survives.

It is nevertheless true that the nineteenth century saw a general growth of skepticism, not as regards therapy only but to a vastly greater degree as regards the whole basis of medical theory. New facts and new attitudes replaced traditional views, as science penetrated farther and ever farther into a realm once regarded as the special domain of art. The consequent revolution was more profound than anything the twentieth century has yet disclosed, by which I mean that the distance traversed in the march of human thought was enormously greater. The century began with Hippocrates, on whom Laennec wrote his dissertation, still firmly lodged in his lofty place as teacher and guide; at its close, indeed long before its close, Hippocrates, except as the voice of conscience in professional ethics, had fallen into the hands of the historians. His practical interest had by then evaporated.

One of the sources of confusion in tracing such developments (in the nineteenth century as in earlier periods) is the common attempt to see it solely in terms of individual contributions, and to see the individuals as good or bad, clear-headed or bemused, enlightened or reactionary. Andral, who normally figures as one of the heroes of the history books, has been shown in his work on tuberculosis as reactionary in a high degree. Still worse, he attempted to revive the whole outmoded business of humoralism generally. Yet was this, after all, an unredeemed and measureless folly? We know, of course, that he was a pioneer haematologist. Beyond this, he slowly evolved, in the setting of what would now be called clinical investigation, a set of hypotheses about the functions of the circulatory system which

can be read today with no little respect. Wunderlich, while waging war on the so-called specificists, created modern clinical thermometry and gave his opponents a new weapon. Back and forth across the line which divides the righteous from the damned, the moderns from the ancients, back and forth and back again, these already legendary figures step and turn, making it difficult to follow the mazes of their dance. This is only, of course, because our ears are not attuned to the music to which they moved. Rich and complex and fascinating is the elucidation of their movements and the understanding of their progress. I am reminded of the bewilderment of C. M. Young contemplating a quite different aspect of nineteenth century English history, over the "warfare between Radicals who upheld Factories and Workhouses, Tories and Chartists who abhorred them both, infidel Benthamites leagued with Conservative Anglicans against dissenting manufacturers, landowners denouncing the oppressions of Lancashire, and cotton masters yearning over the sorrows of Dorset." The history of science and of medicine is similarly complicated, and made all the more interesting, by the mixed motives and labyrinthine courses of those who brought us to the twentieth century. The wonderful century which preceded ours did not achieve its wonders by following a straight line of development, antiquity falling away behind as modernity loomed before it.

By the end of the eighteenth century, well-educated doctors everywhere were convinced that experimentation was profitable and that science would throw a broadening shaft of light upon their labors. It had even been established, at Göttingen, that research might be considered as the duty, and not the indulgence, of the academic physician. John Hunter had inspired a school of imitators. The profession at large was nevertheless the old profession still, and the medical educators had made no more than a tentative start in changing it because they themselves were firmly rooted in the past. It was still true in England that the more old-fashioned a medical education might be (and nowhere in Europe was it more old-fashioned than at Oxford and Cambridge), the more highly it was respected and the more richly those it qualified were rewarded. Empiricism dominated medical thought and contrived, on occasion, to draw contemporary science to its support. Sir Gilbert Blane was sure that Boerhaave had been right to prescribe iron in the treatment of anaemia; he was equally sure that Boerhaave's view that blood contains an iron pigment was groundless—blood had recently been certified free of iron by Fellows of the Royal Society. It was clear to Blane, therefore, that much of contemporary theorizing would be useless were it not for the fact that it led from time to time to clinical trials and chance discoveries. He had no real faith that animal economy, much less human physiology,

could be made to yield its secrets and to contribute directly to the advance of medicine. Instrumentation was as yet in a primitive state and the microscope was subject to technical limitations which made it an object of suspicion to many. Much was hoped for from chemistry but comparatively little had been achieved. Of the sciences on which medicine relied the most hopeful, for the moment, was pathological anatomy. When Sir Henry Halford, Queen Victoria's physician at the beginning of the reign, came to write an obituary of Dr. Matthew Baillie, he recalled that Baillie had made much of physical signs in his diagnoses and suggested that this procedure could be of use only to those, like Baillie, whose knowledge of pathological anatomy was extensive. He did not recommend Baillie as a model for imitation, taking it for granted that few physicians would qualify. In any case, a doctor's main business (and here the venerable royal physician undoubtedly spoke for his generation) was solely with symptoms and their history.

Across the Channel, however, the attempt to correlate both symptoms and signs with post-mortem findings was proceeding apace. Bichat had given an early impetus to tissue pathology. The French clinical school, with Laennec at its head, made pathology the most important business of the doctor. The invention of the stethoscope and the re-introduction of Auenbrugger's percussion rendered the living subject susceptible to direct investigation. A crude form of statistics was requisitioned by Pierre Louis and others to assist in the work of correlation and to assess, as Laennec also sought to do, the value of various forms of therapy. Meanwhile the battle raged over the specificity of disease, pathological diagnosis contributing a new set of criteria for the delineation of species.

However the lines might shift in the great fight about ontology, clinicians continued blithely to observe, to describe, and to define an increasing number of disease entities—in Paris, in London, in Dublin—and a score of eponyms remind us that the first half of the nineteenth century was a golden age of clinical and pathological observation.

The surgeons played a lesser, but nevertheless an important role in this period and it would be wrong to assume that they were waiting in the wings for the introduction of anaesthesia. On the contrary, they were extraordinarily active, especially in the orthopaedic, plastic, and gynaecological fields, as well as in ophthalmology.

Experimental physiology and pharmacology, in the hands of Magendie and his disciples, of whom the most distinguished was Claude Bernard, were later in developing and more limited in their immediate influence. It was nevertheless early apparent, to those who had eyes and could see, that the

physiological, and subsequently the chemical, laboratories would enlarge in every direction the physician's knowledge of the great functions of life and would give him, sooner or later, a new approach to disease. The shadow of Liebig stretched across the whole of Europe.

Slowly at first, and then more quickly and obviously, the growing points in medical advance shifted to the basic science sector; and as this occurred, and as the century marched on its way, German medicine began to acquire the dominance which gave the second half of the century its characteristic pattern.

Meanwhile, however, England had achieved, by means largely social, political, and technical, with inspiration partly medical and partly (odd as the combination may sound) Benthamite and religious, the greatest life-saving advance of the nineteenth century in sanitary reform. The sanitary movement was by no means limited to England but its first and perhaps its greatest earlier triumphs were British. Thence it spread throughout the Western world.

Much of this development took place, of course, long before the advent of bacteriology. When the great new era opened, in the 'sixties, 'seventies, and 'eighties, France and Germany shared the principal honors. The accumulating evidence of living contagion had been summed up shortly before by Henle. Pasteur, Koch, and their pupils did not long delay their entry on stage. What is ordinarily forgotten is the fascinating chapter which goes before, in its likeness to Pasteur's chapter almost uncanny, which tells the story of living contagion, mostly fungal, in the plant kingdom. Since a botanist, as we were reminded by another speaker, discovered the first of the filterable viruses at a later date, one might suppose that the plant pathologists would be worth watching now. Certainly on two previous occasions they have led the way.

The introduction of anaesthesia, to which I shall refer again, was complemented by Listerian antisepsis and asepsis, and surgery flourished amain. The limitations which still remained at the end of the century are clearly suggested, not only by Dr. Keen's brief account in 1901 of progress to date in brain surgery, but also by his description of rib-resection for empyema as still the major triumph in thoracic surgery.

American contributions to the advance of medicine in the earlier nineteenth century are usually, and correctly, supposed to have been largely practical in character. In the earliest stage of its development, American medicine (so the story goes) so far as it excelled its nonprofessional or half-professional beginnings and rose above the crudities of a raw new land, was chiefly distinguished for its contributions to surgery. Leaving aside the

names of Benjamin Rush and a few others—remembered almost as much for their political and patriotic efforts as for their medical endeavours—the greatest names in the early pages of the history of American medicine are the names of surgeons. It is at any rate beyond doubt that the most remarkable contributions to knowledge and practice were in the surgical domain, which is not quite the same thing. Anyhow, Ephraim McDowell, Valentine Mott, and Marion Sims had few if any rivals on the side of physic.

Why was all this so? America, it has been said, was a land of practical men, of artisans and mechanics, of doers rather than theorizers. It was therefore a land of surgeons. The same ingenuity in mechanical contrivance which was proving so beneficial in industry was exhibited also in the operating room. Americans were also thought to be impatient, prone to gamble, willing to take a risk. They were consequently ready to perform, or willing to submit to, heroic operative procedures.

I have sometimes been tempted to imagine that American surgery was original and bold partly because it was isolated in some measure from the surgery of Europe and was therefore, quite simply, freer. Like other developments in American society, it was not so firmly pressed upon by tradition as was European surgery. Physic, on the other hand, being far more dependent on theoretical concepts and more sophisticated in its advance, was still the trade for Europe. This view of the matter explains very little and is perhaps not altogether true even within its limits.

For one thing, European surgery of the same era was far from timid. For another, I have now formed the impression that there was little to choose between the better American surgeons and the better American physicians as regards European education, cosmopolitanism of outlook and knowledge of international medicine. Surgical boldness was not really sustained by a sort of blessed ignorance of European refinements. We are likely to forget that Ephraim McDowell, whom we regard as a backwoods surgeon of great native courage and natural sagacity, had been a student in Edinburgh. In much of his best work Valentine Mott was directly in the Hunterian tradition. Listen, too, to Oliver Wendell Holmes reporting to Harvard students what the old men used to tell the younger ones in Boston.

> Dr. Benjamin Waterhouse, whom I well remember, came back from Leyden, where he had written his Latin graduating thesis, talking of the learned Gaubius and the late illustrious Boerhaave and other dead Dutchmen, of whom you know as much, most of you, as you do of Noah's apothecary and the family physician of Methusaleh, whose prescriptions seem to have been lost to posterity. Dr. Lloyd came back to Boston full of the teachings of Cheselden and Sharpe, William Hunter, Smellie and

Warner; Dr. James Jackson loved to tell of Mr. Cline and to talk of Mr. John Hunter; Dr. Reynolds would give you his recollections of Sir Astley Cooper and Mr. Abernethy.

So the surgeons, too, had been abroad. The surgeons, too, looked to Europe. But there is something else remarkable about this list. Most of the reminiscing Americans were practitioners of physic; and yet, leaving the dead Dutchmen out of account, almost all of the teachers whose names were so often in the mouths of these Boston doctors were London surgeons. How was this? Oliver Wendell Holmes, in his later years, suffered from defects of memory like other old men and his report may not have been completely accurate. It is nevertheless unlikely that he was altogether wrong about what he had heard from the leaders of the Boston profession in the days of his youth. And what he had heard was a group of American "Doctors" talking about a group of British "Misters." American medical men, surgeons included, have been "Doctors" from the beginning; but these were Boston physicians, please you, and their talk was all of London surgeons. Modern American internists who visit London do not return home with their heads full of the wisdom of Ross or Aird or of any surgeon whatsoever; they talk, rather, about Pickering or Dent or about somebody else in their own preserve. Was it merely that the surgery of London in the eighteenth and early nineteenth centuries was so much more interesting than London physic? Probably not, at any rate not to contemporaries, unless they had some reason of their own for transcending the divisions of practice.

Elisha North, of New London, is chiefly remembered today for two things—his description of cerebrospinal meningitis, which Osler regarded as an American medical classic, and the part he played in introducing vaccination. He discovered a case of naturally acquired cowpox, a disease supposed not to exist in America, and was the first to employ vaccine of native origin. North would be thought of, therefore, as a physician. He has other claims on the attention of posterity as well. In 1817 he established the first Eye Infirmary in North America and was reputed to be a skilful ophthalmological surgeon. He also practiced urological surgery and devised a technique of his own for lithotomy. (It was perhaps characteristic of his time and place that the merit claimed for this technique was its relative simplicity in the hands of inexperienced operators.) Elisha North was thus a general practitioner in the broadest sense.

Now in England the surgeon and the apothecary, or low-grade physician, were still more or less distinct, although their link by hyphenation was already producing the surgeon-apothecary, direct ancestor of the modern British G.P. High above both loomed the physician, a gentleman and a

gentleman of learning. His like could hardly be found in America. In the major centers, some men concentrated on surgery and some on physic; but even the lace-at-cuff physician, who liked to imagine himself the Mead or the Heberden of the West, was probably further removed from the modern internist in status and in limitation of practice than the latest Fellow of the Royal College of Physicians practicing in London.

The English tradition of lofty social and educational status had many advantages but unfortunately it excluded much that was good. Such distinguished physicians as Fothergill were beyond the pale; Fothergill's faults were two—he was not the holder of an Oxford or a Cambridge degree and he was a Dissenter in religion. Neither shortcoming would have held him back from the highest reach of distinction in most medical circles in America. The College of Physicians of Philadelphia might have been established earlier than it was had not Fothergill advised William Penn against granting it a Charter. Fothergill could find no place among the Fellows of the Royal College in London and he regarded exclusive Colleges as oppressive and tyrannical.

In America, medicine and surgery were less rigidly separated. This was probably just as well, but it was at any rate inevitable in the circumstances. The character of American physic was affected by this difference in attitude and practice, and if it was sometimes affected for the worse this was not always true. American physicians, differing in this from their European counterparts, were not afraid to use their hands. Even if they did not practice surgery, they were doers; and at those points where physic and surgery came together, this was a distinct advantage. I believe that it long persisted and that it can be traced up to, and even beyond, the middle of the nineteenth century. Let us take one striking example.

Dr. Morrill Wyman, who graduated from the Harvard Medical School in 1837, became Hersey Professor of the Theory and Practice of Medicine and Consulting Physician to the Massachusetts General Hospital. On 23 February 1850, he tapped a patient suffering from pleural effusion, using an exploring needle and a stomach pump, and on 17 April 1850, he aspirated a patient with Dr. Henry I. Bowditch. Bowditch was most enthusiastic in his advocacy of the measure, which he afterwards performed on some three hundred occasions. Thoracentesis had been suggested previously, by Trousseau, but, as Packard has remarked, to Wyman belongs the credit of designing and employing the instruments and technique. He designed a trocar and cannula with a syringe attachment shortly after his first experience. Twenty years later, Paris got round to the rediscovery of Wyman's thoracentesis.

The story of the introduction of anaesthesia, America's greatest contribution to nineteenth-century medicine, is at once more important and more familiar. It is a part, I suppose, of the same pattern. If, in the twentieth century, the United States has taken the leading place in the development of the scientific medical research which was then the province of Europe, in the last age it was chiefly practical and empirical.

Increasingly throughout the nineteenth century European chemists played a part of importance which in our own time has become dominant; the antecedents of this twentieth-century triumph, European and American, I have had no space to examine. The physicists, despite Helmholtz and the ophthalmoscope, had a program for action which remained very largely a dream to be realized later, although to this generalization there are other obvious exceptions. Roentgenology came late and its exploitation belongs to our own age, but several methods were developed for direct visual examination of the cavities and recesses of the body before the old century wore to its end. In a totally different sector, the psychiatrists accomplished humanitarian reforms and participated, a little belatedly, in the differentiation of disease entities; their most important contributions, however, also took form as the nineteenth century merged into the twentieth.

One final note on a similar theme. In his lectures on collectivism, in the famous series called *Law and public opinion,* A. V. Dicey, writing in 1905, had much to say of protective measures, starting with those relating to public health in 1848, which are medical in character; but when he came to his section on equalization of advantages through collectivism, he was too early to have much to report about medicine. Starting in the nineteenth century, this aspect of medical change had also to await fuller fruition in the twentieth.

On the firm basis of nineteenth-century achievement, the work of the present day has expanded in phenomenal fashion. We are accustomed to rehearse the truly glorious accomplishments of the past fifty or sixty years, unparalleled in number and importance. And yet how familiar, in so many ways, are the modes of thought, even in the sciences, of 1900, and how infinitely remote, wrapped in the obscurity of an antique age, are those of 1800! In between lies the wonderful nineteenth century, an era of less explosive development than our own, but one which compresses vastly more, within its own bounds, of the whole long history of medicine.

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THE MEDICAL INSTITUTION OF YALE COLLEGE, 1810-1885†

The first significant fact about the Medical Institution of Yale College is that from its beginning it was part of a collegiate institution. Though for three quarters of a century it was neglected by the Corporation, ignored by its alumni, and misunderstood by the president and faculty of Yale College (for a time a part of its faculty), the connection between it and the College was never broken. Subtly, yet palpably, university status was a guarantee of standards in a period when few medical schools had them, and ultimately this proved to be the foundation on which a modern medical school was built at Yale.[1]

In 1777, shortly before he accepted the Yale presidency, Ezra Stiles outlined a program of medical education in a plan for a university which he drafted for the Yale Corporation.[2] Though neither the state nor private persons came forward with the anticipated endowments, Stiles' hope was not wholly forgotten. A first firm step toward realizing it was taken in 1806 when Rev. Nathan Strong moved in the Yale Corporation that a "Medical Professor" be appointed. Such an appointment, it was quickly realized, presaged a medical department, and Strong's proposal was at once enlarged. There were several reasons why Yale should establish a medical school. For one, since there was no medical school in the state, students who wanted better training than apprenticeship with a local doctor afforded had to journey at least as far as New York or Boston for lectures. In the second place, a medical school would inevitably improve the standard of practice in Con-

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[1] William H. Welch, *The relation of Yale to medicine* (reprinted from the *Yale med. J.*, 1901-1902, *8*, 127-158), is the best treatment of the subject; I relied upon it at many points in preparing this account of the Medical Institution.

The manuscripts cited below are in Yale University, but as some are likely to be moved from their present locations, no indication has been given whether they are in the University Library or the School of Medicine. A fuller history of the Yale Medical School in the nineteenth century is in preparation; it will contain complete bibliographical annotation.

[2] Ezra Stiles, *Plan of a university* (New Haven, 1953), 5-9.

necticut by improving the quality of professional education. Furthermore, a medical school would increase Yale's reputation by promoting the plan for a university which the Corporation had approved 25 years before. And in Benjamin Silliman, trained in chemistry, anatomy, and midwifery by the medical professors of the University of Pennsylvania and Edinburgh, the College had a man of growing stature and reputation, who had hoped to be part of a medical school at Yale and who could take a lead in establishing such an institution. The Corporation approved Strong's proposal and named him and Silliman to negotiate with the Connecticut State Medical Society.[8]

For the curious fact is that the charter of the state medical society in 1792 gave it the power not only to license physicians, but to confer medical degrees. Under this authority the Society had already taken steps to establish educational standards for admission to practice. A program at Yale leading to a medical degree would inevitably conflict with the Society's legal right, which was sure to be the more jealously guarded now that it was threatened. Conciliation and negotiation between Yale and the Society and with the legislature required nearly four years. At its October session in 1810 the assembly incorporated the Medical Institution of Yale College under the joint auspices of the College and the State Medical Society.

By the terms of the charter union there were to be four professors in the Medical Institution; and they were to be nominated by a joint committee of Yale and the Society, and elected by the Yale Corporation. Candidates for practice were to be approved by a joint examining board of the medical professors and an equal number from the Society, with the president of the Society voting in cases of tie. Licenses were to be granted by the Society as heretofore, but the College was to award all degrees, including honorary ones. As a concession to the objection that poor boys would now be unable to get a professional education because of the cost of a Yale degree, each county medical society was authorized to designate one such student annually to attend the Medical Institution gratis.

This joint sponsorship and responsibility is the second important fact about the Medical Institution. For three quarters of a century it condi-

[8] The story of the founding of the Medical Institution has been told many times. See Herbert Thoms, "The Medical Institution of Yale College and the Connecticut State Medical Society," *Conn. Med.*, 1960, *24*, 546-551; Thoms, *The doctors of Yale College* (Hamden, Conn., 1960), 111-147; Walter R. Steiner, "The evolution of medicine in Connecticut, with the foundation of the Yale Medical School as its notable achievement," *Memorial of the Centennial of the Yale Medical School* (New Haven, 1915), 11-33; Connecticut Medical Society, *Proceedings* (Hartford, 1884), 133, 138, 143, 148, 154, 155, 161, 172, 178-179; Benjamin Silliman, Origin and Progress of Chemistry, Mineralogy and Geology in Yale College, IV, 61-62, Ms.

tioned and colored the work and, indeed, the very existence of the school. In the beginning it was a source of strength, for it attached the interest of the Society to the Institution; but finally it became a constraining influence, checking the school's capacity to incorporate the new sciences into its curriculum and to adapt to changing conditions of medical education.

Two years were required for organization. A building was secured at the corner of Grove and Prospect Streets, originally intended, it was said, for a hotel but readily converted to school needs with a lecture hall on the top floor, a dining room, space for an anatomy laboratory in the basement, and student rooms everywhere. Behind the school a botanical garden was laid out. Regulations for student life were adopted comparable to those governing Yale undergraduates—meals in commons, Sunday church and daily prayers, strict curfews, and punishments for a long list of offenses and pranks from heresy and assaults on the faculty through duelling and lock-picking to "hallooing, singing, loud talking [and] playing a musical instrument" during study hours. These regulations proved to be unenforceable, and the scheme of collegiate discipline in the medical school was soon abandoned.[4]

The most important task of organization, of course, was that of selecting a faculty. Silliman was on the ground and was named professor of chemistry and pharmacology. Eneas Munson, the octogenarian doyen of the profession in Connecticut, was elected professor of materia medica and botany, but he never lectured and his duties were discharged from the first by Eli Ives, who had been one of the Medical Society's principal negotiators from 1806 to 1810. For anatomy and physiology the choice fell upon a young college tutor, Jonathan Knight, who had no qualifications for teaching those subjects except native ability and promise but was persuaded to prepare for his work by studying two winters at the University of Pennsylvania.

To complete the faculty the sponsors turned to Nathan Smith, professor of medicine at Dartmouth, probably the ablest and best known physician and surgeon in New England. Trained by country practitioners, with a medical degree from Harvard and a year's study at Edinburgh and London, Smith had had two decades of experience in practice and teaching. His rugged common sense, coupled with manifest power, forcibly struck his contemporaries, accustomed to speculative systems and rolling rhetoric; and some of his strongest recommendations were from young Yale graduates in his classes at Hanover. Fortunately for the New Haven school, Smith was ready to leave Dartmouth. He was tired from overwork and weary of

[4] *Ibid.*, 66-67; *Laws of the Medical Institution of Yale-College* (New Haven, 1815); Yale Corporation, Prudential Committee, Records, V, Jan. 6, 1814, Nov. 6, 1817.

battling the legislature for funds and a reasonable anatomy act, and longed for the leisure to study. Just when he was about to accept the Yale offer, President Dwight objected, alarmed by reports of Smith's early deistical opinions, but Smith made a satisfactory explanation, and he was duly appointed professor of the theory and practice of medicine, surgery, and obstetrics. He was soon so busy, however, that he had to surrender obstetrics, in which, after a short time, Jonathan Knight offered private instruction.[5]

The Medical Institution opened in 1813. In the first year the course was six months long but was reduced at once to five. Competition from schools with shorter courses soon brought about a further reduction of the term to four months, from October through January—a change recommended as economical to students, since it lessened their expenses for heating their rooms. The courses were taught almost entirely by lectures, as the charter required, with no opportunity for recitation and discussion. Since the students were not divided into classes and the professors' lectures were revised little between one year and the next, the principal advantage to a student in taking a second course was that it fixed the material more firmly in mind. Nathan Smith's methods were an exception to this way of teaching, however. He lectured on his cases, stating what he knew and admitting what he did not, he made his points with models and illustrations, he allowed students to question him, and he did it all without flourish, in the plain, straightforward speech of his New Hampshire hills.

The necessary adjuncts of medical education were provided in the new institution. The chemistry laboratory in the College was enlarged to accommodate the medical students. There was an anatomical museum, to which Nathan Smith added his specimens and where, in the 1830's, were deposited those sent home by Peter Parker, an alumnus, who was a medical missionary at Canton. The medical library was small but growing—it was increased in 1833 by a bequest of 250 volumes from a retired naval surgeon, Lewis Heermann[6]—and students might borrow from the College library and use the personal libraries of the faculty. But not until several years after the opening of the New Haven Hospital in 1833 were weekly clinics held there—a service which had frequently been cited as a reason for establishing the

[5] Thoms, *Doctors of Yale College*, 123-147; Harold S. Burr, "Jonathan Knight and the founding of the Yale School of Medicine," *Yale J. Biol. Med.*, 1929, *1*, 327-343; Knight, *A lecture, introductory to the course of lectures in the Medical Institution of Yale College, September 29, 1853* (New Haven, 1853); Emily A. Smith, *Life and letters of Nathan Smith* (New Haven, 1913); Knight, *An eulogium on Nathan Smith, M.D.* (New Haven, 1829).

[6] Frank L. Pleadwell and W. M. Kerr, "Lewis Heermann, surgeon in the United States Navy (1779-1833)," *Ann. med. Hist.*, 1923, *5*, 113-145.

hospital in the first place. As for material for anatomical dissection, which was a popular measure of a medical school's quality in the first half of the century, New Haven did not provide that ready supply Smith had expected: indeed it was rumored that the professors and students systematically removed bodies from Grove Street Cemetery to the medical school cellar via a secret tunnel under Prospect Street; and there was at least one spectacular case of grave-robbing in which an armed mob besieged the school for two nights in 1824.[7] Ten years later, however, prominent families were permitting post-mortems to be performed, and the Medical Institution announced it could supply students with "as many subjects as they may require."[8]

How long a student spent in formal studies varied with the qualification he wanted. Every candidate for practice was required to spend three years in professional study with an experienced physician (two if he had already been to college), and he had to take one course of lectures at the Medical Institution during this period if he wanted a license, but two (of which one had to be at Yale) if he wanted the degree of doctor of medicine. All candidates were examined orally by the joint board of the Medical Institution and the State Medical Society. That these examinations were not necessarily routine is suggested by Jonathan Knight's report in 1815 that the committee had examined five men for degrees and nine for licenses and that they were engaged in the business "for almost three days . . . beginning immediately after breakfast and ending at 9 o'clock at night."[9]

Though the Medical Institution and the State Society were equally represented, the examining board was soon dominated by the professors. They were acquainted with the content of the medical courses and the preparation of most of the candidates, who were their students. They never failed to attend the examinations, which were always held at the College, while the representatives of the Society often did not appear. For similar reasons the medical professors steadily assumed more control of their own affairs within Yale. In 1829 the Corporation empowered them "to make such bye laws . . . as the usefulness of that Institution shall require"; and in 1845 the academic professors were formally eliminated from the government of the school.[10]

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[7] Hannibal Hamlin, "The dissection riot of 1824 and the Connecticut Anatomical Law," *Yale J. Biol. Med.*, 1934-1935, *7*, 275-289; Justus D. Wilcox to Phelps Humphreys, New Haven, Jan. 14, 1824, Ms.

[8] Medical Institution, *Annual circular*, 1839-1840; E. J. Wood, "An early Yale medical student, Dr. E. A. Anderson," Beaumont Medical Club, *Proceedings*, 1924-1925, Ms.

[9] Records of the Examining Committee of the Medical Institution of Yale College, Ms; Jonathan Knight to Mason F. Cogswell, New Haven, May 13, 1815, Ms.

[10] Yale Corporation, Prudential Committee, Records, V, April 28, 1829; Medical Institution, *Laws* (New Haven, 1846).

That year the office of medical dean appears in the catalogue for the first time.

Yet for all this the Medical Institution did not prosper. Not even modest endowments came to it—as late as 1880 its total funds did not exceed $25,000. The death of Nathan Smith in 1829 was a heavy blow. None of his successors equalled him in ability: they were able enough New Haven practitioners but no more than that, and their reputations, as contrasted with the national fame of most of the University of Pennsylvania faculty for example, were essentially local. At one period three of the six professors were brothers-in-law, who seemed to regard the school as a kind of family association—to the understandable irritation of their colleagues. And on top of this, the Medical Institution faced from competition from new schools throughout the country which offered degrees for less money, time, and study, and institutions in New York and Boston which provided opportunities for laboratory work and hospital visitation that New Haven could not hope to equal. Yale was thus in the awkward position of being unable, because of its university connection, to compete with the poor schools and unable, because of New Haven's limited clinical facilities, to compete with the best.

As a result, the enrollment, which had been gratifyingly large during the first 15 years or so, began to drop. In 1827, when 20 students were registered in the Yale Law School and 50 in the Divinity School, there were 91 in the Medical Institution.[11] The enrollment did not again reach that figure until the last decade of the century. Furthermore, the area from which the students came contracted. After 1830 the Medical Institution was more and more a Connecticut training school for Connecticut physicians: of 62 students in 1820, more than a third came from outside the state, but of 28 students in 1861, only five lived outside Connecticut. Far worse than this, however, was the low quality of the medical students. Most of Yale's divinity students and many of its law students had bachelor's degrees, but only a handful of the medical students had attended any college. The catalogues show this condition continued through mid-century. Of 38 theological students in 1850-1851, for example, 31 (80 per cent) had a bachelor's degree; of 26 law students, 17 (65 per cent) had been graduated from college; but of 38 medical students, only 10 (26 per cent) had a degree.[12] The condition was of course not local. The fact was, as Professor Worthington Hooker stated in the revealing report of a committee of the American Medical Association in 1851, that "very little of the educated talent of this coun-

[11] Yale College, *Catalogue*, 1827.
[12] *Ibid.*, 1850-1851.

try finds it way into the medical profession." The better prepared students went into the ministry or the law—Hooker's figures showed those professions claiming a significantly higher percentage of Phi Beta Kappas—and few would choose medicine who had even a prospect of advancement in their fathers' counting house or mill.[13] Addressing the Yale medical graduates in 1856, Dr. Benjamin H. Catlin could only express a hope that it was no longer true, as once it was, "that many commenced the study of medicine because they had failed in every other branch of business, or had nothing else to choose; not for any love for the study or the practice of medicine."[14]

To remedy this situation several medical schools and societies agreed as early as 1827 to establish higher standards for admission and graduation. The Yale professors welcomed the move and had their charter amended accordingly. Applicants for admission were now expected to demonstrate "a competent knowledge of the Latin language and some acquaintance with the principles of Natural Philosophy," as well as mastery of English studies. The length of the medical course was increased to three years for college graduates and to four for others; and candidates for a degree had to attend two courses of lectures. But Yale was alone in adopting these reforms. The other schools did nothing, so Yale was soon hopelessly disadvantaged. In 1832 the short-lived experiment was abandoned.

Though the Medical Institution had to bow to the actual conditions of professional education in America, the medical professors did not. In fact, one of the constant features of the school's history in the nineteenth century is the almost unvarying support the faculty gave high standards, and there is not a little foundation for the claim that the Yale Medical Institution did poorly because it insisted on doing well. The faculty knew that four months was too short a period to teach a boy the anatomy, physiology, and therapeutics he needed for practice, and that formal lectures were not the only, or even the best, way to do it. In 1835, therefore, the faculty announced a private supplemental course of instruction to continue through the 16 weeks of the regular winter term of the Medical Institution, and to run for 26 weeks more in the spring and summer. During the winter there would be one recitation in each course each week, but two recitations daily in the spring. In the winter course the professors would supplement and review the material covered by their lectures in the Medical Institution, but in the spring course they would treat additional topics, and instead of didactic

[13] Worthington Hooker, *Report of the Committee on Medical Education* (Philadelphia, 1851, reprinted from American Medical Association, *Transactions*).

[14] Benjamin H. Catlin, *Annual address* (New Haven, 1856).

lectures only, there would be daily textbook recitations, demonstrations, and experiments. The College libraries and museums would be open to students in this private school, and they might attend the spring classes in anatomy and physiology in the Academic Department. "It will be seen from this statement," the announcement continued, "that the object of the plan is to provide for the medical student, the means of acquiring a thorough knowledge of his profession, by placing him under a regular course of instruction through the year, and by affording him, during the whole period of his study, those means of information, which are best furnished by a regularly organized Medical Institution."[15]

Since, with few exceptions, the instructors were the same in the Medical Institution and the private school, it was hard to distinguish one institution from the other. There was in fact little disposition to do so. The private course was announced in the annual circulars of the Medical Institution, and by 1866 it was called in those catalogues the "Yale Medical School."[16] Thus, despite charter restrictions and completely outside charter authority, a year-long course was instituted at New Haven. "In no other way," asserted the catalogue of 1867-1868, "can the student more easily and naturally acquire a clear, exact, practical and comprehensive knowledge of medical science in its present advanced position, than by taking both these courses in connection." This unusual arrangement continued until the Medical Institution itself formally adopted a year-long integrated course in 1875. Some members of the State Medical Society disapproved the supplemental course, and the examiners could not require attendance at the private school for a degree or even, presumably, ask students questions about what they had studied in it. But the private course obviously prepared students better for their examinations and for practice, and at any time about a third of them were enrolled in it.[17]

From the addresses which members of the State Medical Society gave the graduates of the Medical Institution annually from 1840 to the mid-1860's one can learn something of medical education, medical practice, and especially the medical ideal, or what practitioners believed the ideal should be. The speakers' sentiments have a surprising sameness, and relatively little of their commentary or advice had to do with medical learning. Join a medical society, many of them advised, and nearly all urged the beginning doctor to subscribe to a few journals and, if possible, added another wisely,

[15] *Medical Institution of Yale College, Feb. 1835* (leaflet).
[16] Yale College, *Catalogue*, 1865-1866. See also Medical Institution, *Annual circular*, 1845-1846, and an announcement of the "New Haven Private School of Medicine," dated January 1865, entitled *Private Medical Instruction at Yale College*.
[17] Records of Private Medical Class. Yale-College, March 1865, Ms.

to marry a wife intelligent enough to read them first and mark the articles worthy of notice. In more than 20 years only one speaker recommended that a physician should master some single branch of medicine, though without limiting practice to that specialty. Several urged him to dissect whenever he could, and William Wickham Welch explained why it was important to keep records of all cases: "Rest assured, this book of nature in future years you can read with profit."[18] Most of the advice was moral and political. The American medical profession was popularly believed to have been dangerously infected by the rationalistic ideas of the French Enlightenment, and to be materialistic and atheistic. To refute such imputations was the solemn task most of the annual lecturers undertook. Go to church, was their unvarying advice, though one speaker stoutly assured his audience that joining a church did not mean "capitulation."[19] Observe the Sabbath, even to postponing professional calls. "When we are able to heal the sick, cause the lame to walk, and restore sight to the blind," commented one speaker drily, "then we may spend the entire day in that Christ-like employment."[20] Dr. Luther Ticknor warned the graduates of 1841 against "the light dissipating literature of the day . . . the silly, catch-penny trash, at present so abundant, and yet so fascinating;"[21] and Hanford N. Bennett spelled out the warning in 1855: "Instead of Rousseau, Voltaire, Racine, or Madame de Stael, let him read Cruveilhier, Bouillaud, Barthez and Louis among the French; instead of Goethe and Schiller let him read Muller, Wunderlich, Rokitansky, Kolliker and Virchow, among the modern German authors of the highest order of talent."[22] Be a good citizen, the advice continued, support the laws and the Constitution, but to be an avowed partisan or to run for public office was dangerous for a physician. And, above all, shun the homeopaths.

Politics and homeopathy were in fact closely linked in professional thinking in the middle of the century. Physicians were alternately angry and disgusted that state legislatures should open the door to all sorts of practitioners by refusing to require regular licenses. This was simply official ratification of popular ignorance and superstition. To believe, as the legislators seemed to do, that a properly educated profession was a sinister monopoly was in the physician's view democratic nonsense. Several annual addresses were eloquently critical of popular attitudes which sympathized with and supported illiterate bonesetters and herb doctors. Even the clergy

[18] William W. Welch, *Annual address* (New Haven, 1857).
[19] Luther Ticknor, *Annual address* (New Haven, 1841).
[20] Catlin, *Annual address.*
[21] Ticknor, *Annual address.*
[22] Hanford N. Bennett, *Annual address* (New Haven, 1855).

came in for criticism because out of ignorance of science and a vague good will they too often accepted the charlatan and his nostrums equally with the trained physician. Since the physicians could not alter the laws or the prejudices of the public, they were advised to withdraw from public affairs.[53] The doctors' retreat was probably unfortunate, for it opened the door still wider to the very influences they decried, and it decreased their opportunities to direct or even understand the political and social realities which surround the profession.

The decade of 1860 brought intimations of improvement. The public was, in Professor Hooker's phrase, "beginning to be convinced" that an educated and organized profession was desirable and necessary.[54] The stupendous explosion of medical knowledge required a thorough revision of the curriculum and total abandonment of eighteenth century methods. Sensitive to the changes, the faculty began to urge the Yale Corporation to adopt three basic reforms: a year-long course taught by recitations as well as lectures; a graded curriculum, with examinations required for advancement to the next class; and entrance requirements. Each of these was both necessary and practicable, as the faculty's experience in the private school demonstrated—there students recited and were separated into grades. But none of the reforms could be achieved without financial support from the Yale Corporation. Year after year the faculty appealed for the "countenance, encouragement and sympathy" which were so generously given to the other departments of the University.[55]

The claims of the medical school received some support elsewhere in the University. Professor Timothy Dwight (later to be president) in a series of articles in 1870-1871 sketched the principles which Yale must observe to become "a true university." The Medical Institution, he asserted, could no longer depend, as it had so long done, on the devotion and reputation of individuals; it must be a university department, equal in status with the other schools, equally inspired by university ideals, equally cherished by the Corporation, and continuously supported with university funds.

The day is approaching [Dwight went on] when the system of cramming students of this science with six lectures a day, following each other in six successive hours, and, after two courses of this kind of sixteen weeks' continuance, turning them out upon the world to exercise their art, will meet

[53] Pinckney W. Ellsworth, *Annual address* (New Haven, 1854); Henry Bronson, *Annual address* (New Haven, 1863, reprinted in *Yale J. Biol. Med.*, 1934-1935, *7*, 386-399).

[54] Worthington Hooker, *The present mental attitude and tendencies of the medical profession* (New Haven, 1852).

[55] Medical Faculty, Memorial to the Yale Corporation, March 25, 1873, Ms.

as universal condemnation as it deserves. But when it does come, those schools will be recognized as worthy of credit and support, where another and more reasonable system has been established, and students will come to them for an education.[26]

The Corporation, however, was unprepared to do more than appropriate a few hundred dollars for immediate needs, and the Yale medical faculty had the mortification of seeing Harvard put its medical school on an equal footing with the other departments and thus "put *our plans* into successful operation."[27]

Meanwhile the physical plant deteriorated, and financial conditions became desperate. To make space the library was moved out of the medical school in 1865, thus separating it from the students. In the museum there was not enough money even for alcohol for the specimens, and things were so carelessly arranged there that part of an elephant's skeleton was misplaced for several years. Income from endowment—about $1,000 a year—was barely sufficient for minimal expenses; tiny balances—the year 1863-64 ended with $7.67—alternated with ever larger deficits; and year after year the professors accepted I.O.U.'s instead of their salaries, so that the building could be painted or another microscope bought.[28] There was in short little in the promises of the Medical Institution, or even at Yale College, to attract the able and ambitious to medical study or teaching there. William Henry Welch, of the class of 1870, hoped to return to Yale the next fall as a tutor of Greek.

The problem of the Medical Institution had become one that the faculty alone could no longer meet. The Corporation, however, was still disposed to feel that if the medical faculty wanted money, they should beg for it themselves. The faculty tried, but discovered, as they informed the Corporation, that representatives of the College had gleaned the same fields before them. The fact was that no amount of devotion and sacrifice by the faculty could provide the funds that were indispensably necessary. In a strongly worded memorial to the Corporation in 1873 they raised the stark question, "How long, on the present plan, can the Medical Department be continued?"[29] Still not ready to commit itself to the concept of a university medical school, the Corporation voted, as heretofore, a few hundred dollars to quiet the most

[26] Timothy Dwight, *Yale College: Some thoughts respecting its future* (New Haven, 1871), 7, 47-50, 54-55, 61-62.
[27] Medical Faculty, Memorial, March 25, 1873, Ms.
[28] Charles A. Lindsley, Account of Expenditures, 1863-1869, Ms; Medical Faculty, Minutes, I, Feb. 2, 1864, Aug. 1, 1866, Sept. 3, 1867; Dean's Account Book, 1869-1881, Ms.
[29] Medical Faculty, Memorial, March 25, 1873.

clamorous creditors and fill the most urgent needs. But finances worsened, faculty appeals continued, and in 1875 the Corporation responded by designating their treasurer to manage the financial affairs of the Medical Institution.[30]

This acceptance of responsibility was broadened two years later when the Corporation bought property for a dispensary. Though not irreversible, this step seems in retrospect to be of the greatest significance. The relation of the Medical Institution and the New Haven Dispensary, which was opened in 1872, was not close, and the medical professors were in the unsatisfactory position of being guests in the institution whose facilities they needed for their work. By 1877, when more than 5,000 patients a year were receiving treatment there, the Dispensary had outgrown its quarters. The medical professors therefore suggested that the Corporation buy a property adjoining the school and rent it to the Dispensary at a nominal figure, "on condition that the Medical Faculty shall have the right to nominate the medical attendants, and the medical Students of the Institution shall have the privilege of viewing the medical and surgical practice." The Corporation acquired the property, the Dispensary physicians were made instructors in the Medical Department, and the New Haven Dispensary thus became an integral part of the school's program of clinical teaching.[31] What this meant in the long history of the medical school was that the Yale Corporation had at last made a progressive commitment to the future of the school. It was not the last.

Thus it seemed in the later 1870's that the Yale Corporation was ready to support the Medical Institution. The faculty, therefore, confidently adopted a series of educational reforms. A year-long course was established, instruction in the second term being by recitation and textbook as well as by lecture. Written examinations, three hours long, replaced the oral examinations by the joint board, and similar examinations were required in individual courses two years later. Despite the certainty of a disastrous drop in enrollment, the faculty announced specific requirements for admission.

The permanence of these changes and the achievement of others equally desirable were assured by a new charter, obtained from the legislature in 1879. Unlike its predecessors, it did not limit the number of professors; it allowed the faculty to determine the length of the term and methods of instruction; it quietly withdrew the right of the county societies to appoint worthy gratuitous students; and it contained the all-important provision

[30] By-Laws for the Government of the Medical Department of Yale College, 1875, Ms; Charles A. Lindsley, Estimate of Expenses for ensuing Year, Sept. 18, 1875, Ms.
[31] Medical Faculty, Minutes, I, June 19, July 21, 1877, Jan. 14, 1879; F. B. Dexter to Charles A. Lindsley, June 29, 1879. Ms.

that the agreement between Yale and the Medical Society might be abrogated by mutual consent, without further legislative action. It even changed the school's name from the Medical Institution to the Medical Department of Yale College.

Freed from the restraints of the old charter, armed with the authority of the new, the Yale Medical Department adopted still other basic reforms. The course of study was lengthened to three years, each year consisting of two terms of eighteen weeks each. Admission examinations were required. By the separation of physiology from anatomy, an additional professorship was created. Teaching would hereafter be by methods "more and more personal and less didactic."[83] Specialists from New York and Hartford were invited to lecture on particular subjects, such as the eye and ear, insanity, and forensic medicine. When a committee began to look for a professor of materia medica in 1883, they were assured that they were "not restricted to the residents of New Haven.".[83]

The reforms revived pride and confidence in the Medical Department, both in New Haven and elsewhere. The faculty expressed faith in their program and its future in a report of 1880:

> The rapid rationalization of medicine is throwing more and more weight upon the earlier, more fundamental and scientific parts of medical education. This is what the medical department here, by its close connection with the other departments of the university in a university town, and the aid, recognition and encouragement which an academic community alone affords, is peculiarly well situated to supply. There is also the possibility which will in time be more and more improved throughout the University of making the teaching in any line in any department accessible to the students in another, instead of duplicating the chairs. These are the advantages which we have and which the well known schools in larger cities have not. On the other hand the clinical facilities afforded by the hospital and dispensary are steadily growing.
>
> It is possible to make here, in the near future, a medical department, good in its clinical and preeminent in its scientific instruction. A school, whose distinguishing mark was the extent to which it carried its scientific instruction and its facilities for making the results of scientific investigation tell upon medical practice, would have a range of influence far transcending the numbers who frequented its class rooms. And this extent of influence constitutes its claim for support beyond the fees of its students. Nowhere can generous minded men place money with better grounded confidence that it will do its utmost for raising medical education and increasing the power of medical practice.[84]

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[83] Medical Faculty, Minutes, I, May 22, June 12, 1879.
[83] *Ibid.*, II, March 8, 1883.
[84] *Yale College in 1880* (New Haven, 1880), 9-10.

The immediate result of these improvements, as the faculty had foreseen, was a drastic drop in student enrollment: many students simply could not meet the new requirements. The faculty, however, never wavered in support of their announced convictions, though they did lower the tuition, hoping in this way to bring in a few more students—an action which only made financial condition worse.

Needless to say, those who had opposed the changes or doubted their wisdom cited the new plight of the Medical Department in justification. One of these was the professor of pathology, Moses C. White. An active member of the State Medical Society, he resented the weakening of the Society's influence in the Medical Institution, and formally opposed his colleagues' appeal to the Corporation in 1882 calling for increased university support. All that was needed, in his view, was a re-dedication to the principles and spirit of the old union between Yale and the Society, and as for the talk of making Yale the equal of medical schools in New York and Boston, that was idle dreaming.[85] White's objections found some willing listeners. Some of the Corporation doubted, as he did, that New Haven was large enough to support a great center of clinical instruction. Others feared the costs, which seemed to grow larger every time the faculty discussed their needs. President Dwight, contemplating them, is said to have asked plaintively, and perhaps hopefully, whether bacteriology was not "a passing phase of learning" in which there would "be little interest . . . a few years from now."[86] Possibly as a result of such doubts the Corporation in 1884 made no appropriation to the Medical Department for the next year.[87]

This unexpected action was received with apprehension and dismay. The faculty soon learned what it meant. The Yale Corporation had accepted a responsibility for the Medical Department, which it was now discharging, however modestly, yet the State Medical Society, which was a joint sponsor, did nothing. The Corporation believed that if it was to support the Department, it should control it. The faculty agreed, and cooperated warmly and swiftly to effect the change, arranging for the Society to terminate the agreement of 1810 and so make the medical school wholly and integrally a Yale institution.[88] Thus Yale's support of the department had led to university control, and control would lead to ever-widening acceptance of responsibility and ever-increasing support.

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[85] Medical Faculty, Memorial to the President and Fellows of Yale College, a confidential printed memorandum submitted in June 1882; Moses C. White to Prudential Committee, June 21, 1882, Ms.

[86] Charles J. Foote, "Early years of bacteriology in the Yale Medical School and in the City of New Haven," *Yale J. Biol. Med.*, 1940-1941, *13*, 309-314.

[87] Medical Faculty, Minutes, II, April 24, 1884.

[88] *Ibid.*, April 26, May 17, 27, June 12, 1884, May 21, 1885.

The next year—1885—President Porter asked for a plan of re-organization, and the faculty, now encouraged and emboldened, responded with a request for $400,000 to endow instruction in the rapidly expanding medical sciences. These, they explained, were "not luxurious embellishments . . . not even the anticipated needs of the future. They are the needs of the present time, strong and uninterrupted. . . ." A strong *university* medical school was a guarantee that medical study at Yale would be pre-eminently scientific, while the clinical facilities at New Haven, which were deemed "considerable and satisfactory," would insure that science was balanced by practice.[39] These sentiments were enlarged upon two years later by William H. Welch, professor of pathology in the newly established Johns Hopkins University. Medicine should always be taught as a department of a university, Welch declared in an address at Yale in 1888, but such a union must not be merely formal. "There must be a union in spirit as well as in name," he continued. "The influences of university methods and idea [*sic*] must manifest themselves in the medical department. . . ." A university school, he thought, could flourish at New Haven: Yale had laboratories in all the natural sciences, the town had the favoring atmosphere of a university community, while as for the objection that New Haven's population was too small, it was methods of examination that made for good clinical teaching, not the number of patients. To reap the full advantages of its situation, the Yale Medical Department must have endowments. "In no other direction could this university expand with greater promise of usefulness and of renown," Welch concluded, "than in the line of liberal support of the highest and most scientific medical education."[40]

Yale took up the challenge. Repeating Dr. Welch's arguments at an alumni meeting at Bridgeport two years later, Dr. Gould Shelton flatly declared that Yale's position was "most favorable for the building up of a school of the highest standard," and he called on graduates for financial support.[41] Ultimately this was given in generous measure. To those who knew Yale, the decision of the Corporation to accept the Medical School as an integral part of the University and the commitment of the alumni to support it were assurance enough that the future of the Medical Institution in the twentieth century would be secure.

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[39] Report of a Committee of the Medical Faculty on the Reorganization of the School, 1886, Ms.

[40] William H. Welch, "Some of the advantages of the union of Medical School and University," *New Englander and Yale Review*, September, 1888.

[41] Gould A. Shelton, *The claims of the Yale School of Medicine on the university alumni* (reprinted from the Records of the Alumni Association, 1890).

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THE YALE SCHOOL OF MEDICINE IN THE TWENTIETH CENTURY†

An anniversary is an occasion for rejoicing and reminiscence. It is also an occasion for taking a hard look at where one stands and for facing up to the challenges of the future. These are the assignments my colleagues and I have set for ourselves.

The history of the Yale School of Medicine over the first century, after a charter was granted to the Medical Institution of Yale College by the General Assembly of the State of Connecticut on 28 October 1810, precisely 150 years ago today, differed from that of many medical schools founded in the early part of the nineteenth century. Adoption by an established liberal arts college gave the School stability and resources which many of those created over the following 50 years never attained. It was the first step in the fulfillment of Ezra Stiles' dream of Yale as a great university. Furthermore, it had the unusual advantage of being founded with the blessing of the local medical community, as its charter was granted jointly to the College and the Connecticut State Medical Society. Thus, it escaped the struggles for control and satisfaction of personal ambitions which characterized the early history of many schools founded as proprietary institutions.

The progress of the Medical Institution of Yale College and, after 1887 the School of Medicine of Yale University, during the first hundred years will be reviewed by other speakers and recorded in a volume to be published within the year. Let me pick it up in 1910 when George Blumer, a physician with national reputation and a clear vision of the University's future role in medical education, was appointed professor of medicine and dean. The fortunes of the School were, at that moment, at a low ebb. This was the beginning of the renaissance of medical education in the United States. Under the leadership of William Henry Welch, a graduate of Yale College in 1870, the Johns Hopkins School of Medicine was setting a new pace; other leading schools had responded to the challenge, but Yale was lagging behind. Poorly supported by the University, morally and financially, a school which had stood among the best in its early days was losing ground rapidly. The

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† Presented at the Sesquicentennial Anniversary Program of the Yale University School of Medicine.

Corporation was faced squarely with the necessity for making a decision as to whether it should continue to operate a good liberal arts college with loosely appended graduate and professional schools or should become a university in practice as well as in name. Not without controversy it reached the latter decision.

The condition of the Medical School at the time was such that more than policy decisions and good intentions were necessary. It was housed in an uninspiring and obsolete building on York Street. The faculty was made up largely of local physicians who volunteered their services to give a few lectures or to demonstrate patients at the New Haven Hospital where students were little more than tolerated, despite the fact that the Hospital had been founded 84 years earlier by the faculty for the stated purpose of providing opportunity for clinical experience. Entrance requirements were changed from a high school diploma to two years of college work in 1910 and practically anyone who met them was admitted. During the decade 1910-1920, there were 128 graduates, an average of 13 per year. The budget for the academic year 1910-1911 was $43,311. A sign found in the basement of the York Street building which I now have hanging in my office reads "Dean's Office, Hours 8:30-9:30 a.m. Wednesdays."

The decade 1910-1920 may be characterized as one of unrest and struggle for improvement in the face of inadequate resources. For holding the school together and prodding the administration of the University into action during this difficult period, too much credit cannot be given to Dr. Blumer and a small group of devoted colleagues. Notable among his achievements were the appointment of several men, among them Samuel C. Harvey, Milton C. Winternitz, and Charles-E. A. Winslow, who were destined to play leading roles in the years to follow.

The importance of having the right man in the right place at the right time was never better demonstrated than in the appointment of Dr. Winternitz as dean of the School of Medicine in 1920. Aggressive and imaginative leadership was needed. The School had fallen so far behind that drastic measures were indicated. It does not detract from his achievement to note that the opportunity was ripe. With the strong support of President James Rowland Angell, who came into office in 1922, the School moved forward by leaps and bounds. A few of the leaps may have been miscalculated and some of the bounds landed on people's toes, but the ultimate results were good. In 1934 Dr. Welch said: "There is nothing in modern medical education so remarkable as the recent transformation of the Yale School of Medicine from the old type into a modern medical school. The process has taken place with incredible rapidity and it has been complete. The Yale School of

Medicine now ranks with the best in the country. Any list of half dozen leading schools in the country must include Yale."

The significance of the Brady gift, which built the Brady Memorial Laboratory in 1917, and of the Sterling gift, which made possible construction of the Sterling Hall of Medicine in 1923, cannot be overestimated. There has been too much loose talk about bricks and mortar in recent years, which has led some people to believe that it is almost sinful to give money for buildings. But medical research had moved away from bedside observation and into the laboratory, and without these buildings, which provided the faculty and students with a decent place in which to work, little would have been accomplished. The move from the dingy, depressing quarters on York Street to new quarters in the Hospital neighborhood was symbolic. There was new life. The spirit was contagious and able young physicians and scientists and brilliant students were attracted in increasing numbers.

Gifts for endowment which began to flow in at that time were of equal importance. They told the world that here was an institution worthy of a substantial investment. A gift from the General Education Board of the Rockefeller Foundation made possible the inauguration of full-time salaried faculty appointments in clinical departments. This development, which took place at Yale and several other schools at about that time, has probably had greater influence on medical education and research in the United States than any other during the twentieth century. It brought the science of medicine to the bedside. It gave status to a group of men who could communicate with the basic scientists and apply their discoveries to problems of diagnosis and therapy. For the student, it made transfer from the laboratories of the basic medical sciences to the hospital wards a logical sequence instead of a series of unrelated experiences.

The influence of these events on the parallel growth of the New Haven Hospital cannot be overestimated. I think it is fair to say that in 1920 it was a rather ordinary small town hospital of 270 beds. Some of the buildings in use had been in service when it was a military hospital during the Civil War. The one operating room, the Farnum Operating Amphitheatre, had been erected in 1888. Pathological laboratories, erected during the First World War, were one-story, tar-papered barrack buildings. During the following 15 years, with the aid of funds raised and contributed by the University, it was transformed into a modern hospital.

This was also the period during which the fertile mind of Dean Winternitz, with the strong support of President Angell, visualized the transformation of the area surrounding the Medical School and Hospital into the Human Welfare Group which was to include the Institute of Human Rela-

tions, the Law School, the Divinity School, and related social and biological sciences. Only the Institute of Human Relations materialized, but that alone was a major achievement because it brought into close relationship with the medical sciences the Departments of Psychology and Anthropology and provided a firm foundation for development of the Department of Psychiatry and the Child Study Center.

Dr. Winternitz retired from the deanship in 1935 and was succeeded by Stanhope Bayne-Jones, a graduate of Yale College in 1910, who had joined the faculty as Professor of Bacteriology three years before. The years of depression and war which followed were a period of consolidation. An eminent faculty had been assembled, brilliant young men and women came from all over this country and abroad to work in the laboratories and clinics, graduates assumed positions of responsibility in other faculties, and the footnote, "from the School of Medicine of Yale University," appeared with increasing frequency in the leading medical and other scientific journals.

One of the most important events in this period was the construction of the Medical Library which was opened in 1941. This made possible the consolidation of the magnificent historical collections of Harvey Cushing, Arnold Klebs, and John Fulton as well as the organization of one of the best working libraries for the medical sciences in the world.

Progress was interrupted by the Second World War. Dean Bayne-Jones and a substantial part of the faculty entered military service. The 39th General Hospital, organized at Yale, made a brilliant record in the South Pacific. Those who remained did double duty to keep the School in operation under an accelerated program and made notable contributions to the war effort through their research. Francis Blake divided his time between the Dean's Office, the Department of Medicine, and the Army Epidemiological Board in Washington.

He was succeeded in the deanship by C. N. H. Long, then Professor of Physiological Chemistry, who was responsible for reassembling a strong faculty and restoring operations to an even keel during the post-war years. Relations between the School and the Hospital, renamed the Grace-New Haven Community Hospital when the New Haven and Grace Hospitals were consolidated, were adjusted on a more satisfactory basis. The Memorial Unit, which increased the capacity of the Hospital to 658 beds, was built. With this expansion and the opening of the Veterans Administration Hospital of 880 beds in West Haven, adequate clinical facilities for instruction and research were no longer a problem.

It was my privilege to succeed Dr. Long in 1952. By this time, the place of the School of Medicine in the University and in the scientific world was

well established. The challenge was to maintain a superior program of instruction and still take advantage of an expanding opportunity to develop further as one of the leading centers of medical research. It was apparent that the basic essentials to meet this challenge were available. An entering class of 80 students could be selected from among over 1,000 applicants, and those admitted had scores on the Medical College Admission Test which placed them among the top 15 per cent of all students applying for admission to medical schools in the United States. In such a group, there was no lack of intellectual or personal quality. The faculty was competent and devoted but needed strengthening in spots.

Several deficiencies in physical facilities were only too apparent since there had been practically no construction of medical school buildings since before the war. Thanks to the generosity of The Commonwealth Fund, the students, who had lived under deplorable conditions, are now quartered in the Edward S. Harkness Memorial Hall and the Mary S. Harkness Memorial Auditorium is approaching completion. Laboratories for the Departments of Anatomy, Biochemistry, Pharmacology, Epidemiology, Internal Medicine, Pediatrics, and Radiology have been expanded and others remodeled and improved. In cooperation with the State of Connecticut, a new psychiatric hospital is in the planning stage. Improved and expanded quarters for experimental animals and for the Department of Microbiology are under construction.

Over the past decade the Departments of Biochemistry, Physiology, Pharmacology, Internal Medicine, Obstetrics and Gynecology, Radiology, and Public Health have been reorganized under new leadership. A Department of the History of Science and Medicine has been established. The budget, over half of which is now derived from gifts from outside sources for research, has increased from $2,500,000 to $6,500,000 and the endowment, from $13,300,000 to $18,700,000.

I would not want to leave the impression that the requirements for either facilities or endowment, if the School is to take full advantage of its potential, are satisfied. I doubt that they ever will be. New opportunities for the advancement of the frontiers of medical science become apparent almost daily. These challenges can be met only if men with vision and skill are provided with the laboratories and equipment necessary for their work. One of the early donors to Yale recognized that it was "struggling with pecuniary embarrassments." The situation has not changed.

A major strength of the School over the past 35 years has been the consistency of its educational policy, and no consideration of its present status would be complete without referring to it in some detail. At a time when

the status of the School was such that any deviation from the standard pattern of medical education would have been viewed suspiciously, the faculty had the vision and the courage to embark upon a program which differed from that of any other medical school then in operation. The fundamental concept was, and still is, that medical students are graduate students and should be treated accordingly. Lectures are confined to consideration of material not readily available in textbooks, and instruction in small conference groups with active student participation is emphasized. New opportunities for elective study in fields of mutual interest to the instructor and student have been created. Interest in scientific inquiry is stimulated by providing opportunity for original research under intimate supervision of experienced investigators. Students are encouraged to advance at their own pace, and increasing numbers choose to spend an additional year or summer vacations in concentrated research activity. Examinations in courses have been abolished, and advancement by hurdles, which resulted from memorizing a course and promptly forgetting it, have been eliminated by substitution of examinations on completion of the preclinical and clinical years. The study of medicine is organized so that it follows a logical sequence from normal structure and function, to deviations resulting from internal and environmental influences, to application of this knowledge to prevention, diagnosis, and therapy.

Precise evaluation of any educational program is difficult, but certain indices are encouraging. Comparison of the achievement of Yale students with all the students in the United States who have taken the examinations of the National Board of Medical Examiners shows that the average scores of Yale students are invariably at, or near, the top of the list. Last year 37 per cent made honor grades, as against a national average of 15 per cent.

Those in practice are respected in their communities, and a surprisingly large number have continued their interest in teaching and research. An analysis of the achievement of the graduates over the 25-year period, 1928 through 1952, is of interest. Forty-two per cent of the graduates over the entire 25 year period studied now hold academic appointments on a full- or part-time basis. The proportion of graduates engaged in teaching and research on a full-time basis has increased over each five-year period, reaching 20 per cent for those who were graduated in the years 1948 through 1952. No other school, among the 85 in the United States, can claim a similar record.* I strongly suspect that when those graduating in 1960 have been

* Ebbert, A.: A retrospective evaluation of research in the medical curriculum. *J. Med. Educ.*, 1960, *35*, 637. Weiskotten, H G., Wiggins, W. S., Altenderfer, M. E., Gooch, M., and Tipner, A.: Trends in medical practice. An analysis of the distribution and characteristics of medical college graduates, 1915-1950. *J. Med. Educ.*, 1960, *35*, 1071.

out long enough to get settled, the proportion will be even higher and the influence of Yale University on the progress of medical education and research throughout the world correspondingly greater.

Any measurement of the educational value of a modern medical school cannot be confined to consideration of the achievements of those to whom it has awarded the M.D. degree. Actually, those who are candidates for this degree constitute only about one-half of our student body. The other half is made up of interns and residents in advanced training for specialization, graduate students in public health and the basic medical sciences, and postdoctoral research fellows who come here to obtain experience in research under the guidance of our faculty. This year 120 postdoctoral research fellows from all over the United States and 17 foreign countries are working in our laboratories. Members of the current student body, including the categories just mentioned, attended 221 colleges and universities before coming to Yale and come from 44 states and 25 foreign countries. I mention this fact to emphasize the point that although the contribution of the School in service to the local community and state is substantial, its influence in the scientific world is of equal or greater significance.

While our educational program has grown in an orderly manner, there has been an explosive growth in research activity, and there is every indication that the rate of acceleration will increase. Yale scientists have contributed to every important advance in medical science which has taken place in recent years. It is estimated conservatively that expenditures for medical research in the United States will be tripled over the next decade. Research in medical schools will expand proportionally. This is one of the things that keep university administrators awake nights. Under present conditions, there is a reasonably good balance of emphasis on instruction, research and, in the clinical departments, service. Increased research activity has lead to improvement in instruction. There is a serious threat, however, that balance will be lost. The values placed on research achievement cannot be allowed to become so high that the reward for being an inspiring teacher will become insignificant.

Another by-product of expanding research activity can be a loss of awareness on the part of the faculty, and consequently on the part of the student, that they are dealing with human beings whose health and well-being are influenced by social and emotional as well as physical forces. This is not, however, an insurmountable problem, and experience demonstrates that concern for the patient's emotional problems, as well as his physical disorders, are not incompatable—in fact, when one outweighs the other, the result is poor medicine. A strong department of psychiatry is important in keeping these factors in balance.

Laboratory research alone will not control disease. The results of basic investigations must be translated into clinical practice; better methods of bringing them to the community must be organized, and people must be educated to accept them. These facts were recognized in the establishment of the Department of Public Health in 1915 and are equally valid today. After a period of 45 years, during which the graduates of the program in public health have assumed positions of responsibility for control of disease and organization of health services throughout the world, it is now being reorganized. The basic program will be continued, but will be placed on training physicians in epidemiology at an advanced level to prepare them for positions of responsibility in research and service in universities and in national and international organizations.

No medical faculty can fail to be continually concerned with the quality of service rendered in the hospitals with which it must be intimately associated. The student becomes a physician through day-by-day contact with sick people in the wards and outpatient clinics, and the kind of physician he will become is dependent upon the quality of medical care rendered by those whom he observes. For this obvious reason, association of the School of Medicine and the Grace-New Haven Community Hospital must be fostered and strengthened, to the mutual advantage of both institutions. Their interdependence has been recognized in the organization of the Yale-New Haven Medical Center, which will serve as an instrument for joint planning of functional and structural development and for fund-raising. The master plan for development of the Hospital and related laboratory and teaching facilities for the clinical departments of the Medical School, recently completed, is a landmark in the association of the two institutions. Expansion of the magnitude visualized will only partially meet the demands of the growing community of Greater New Haven but, as smaller hospitals are established in surrounding communities, the Medical Center will become, to an even greater extent, a regional facility to which patients with complex problems requiring special equipment and skills will be referred. In return, it will have to be supported by the larger community which it will serve.

This service element in the activity of the full-time members of the clinical departments represents perhaps the most perplexing problem with which this and every other medical school is faced today. To remain a skillful physician or surgeon, a teacher must continue to assume personal responsibility for the care of a few patients, and the community cannot be deprived of his special talents. On the other hand, when the service factor assumes a dominating position and a so-called faculty is dependent upon its earnings from service for survival, a medical school becomes a trade school and has

no place in a university. In my opinion and the opinion of the majority of our faculty, adherence to the policy of maintaining a strong nucleus of academically oriented faculty members in the clinical as well as the basic science departments has been a major factor in bringing the School to the position of eminence which it enjoys today.

Medical education in the United States has developed to the point where every medical school cannot do everything that every other one does and do it well. Some schools, particularly those associated with state universities, will be oriented to training of physicians for the conditions of practice prevalent in rural communities. Others cannot escape the overwhelming service element involved in the care of patients at several large city hospitals. Others, more intimately related to universities where high standards of scholarship prevail, will adopt the coloration of their parent institutions and will make their greatest contribution in the production of physicians and other scientists who will play leading roles in specialized medical care, teaching, and research.

The Yale School of Medicine finds itself in the latter group and is, for that very reason, faced with problems of curriculum adjustment which some others may avoid or at least postpone. The traditional curriculum of American medical schools was originally geared to the production of physicians who entered the general practice of medicine immediately after graduation and it has not been altered substantially for many years. Methods of instruction and course content have varied, but the list of courses has not changed despite the rapid growth of medical science and introduction of innumerable new techniques of diagnosis and therapy. Furthermore, little attention has been given to the fact that those preparing for specialization now devote three to six additional years to postgraduate training in hospital internships and residencies and obtain the major portion of their clinical experience at that level. As I mentioned earlier, our methods of instruction have been adapted to current trends but I now question whether our curriculum also should not be made more flexible and adapted to the particular career objectives of the type of student with whom we are dealing.

These are but a few of the problems and challenges with which the Yale School of Medicine is faced as it enters its 151st year. Our objective, however, remains perfectly clear—the maintenance and cultivation of a community of scholars who, at various levels of maturity and experience, are learning together. In such an atmosphere, good physicians will be educated, and the frontiers of the science of medicine will be advanced for the benefit of all mankind. This is an effort worthy of a great university.

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MEDICAL RESEARCH AT YALE IN THE TWENTIETH CENTURY†

PREPARATORY EVENTS

To understand the conditions that made possible the great development of research at Yale within the past 50 years we must inevitably look into the preceding century. There were external influences. The fire of European science was burning at its brightest, fed by such men as Ludwig, Pasteur, Virchow, and Cohnheim. William Henry Welch was the Prometheus of American medicine who bore the sacred flame to the newly founded Johns Hopkins Hospital and Medical School. It is of interest here that both he and Daniel Coit Gilman, the President of the new University in Baltimore, were graduates of Yale, and the former repeatedly gave invaluable stimulus and assistance to the then struggling medical school of his alma mater. In a commencement address at Yale as early as 1888 he put it thus: "In no other direction could this University expand with greater promise of usefulness and of renown than in the line of liberal support of the highest and most scientific medical education."

By the 1870's conditions in New Haven were indeed becoming more favorable for the development of the biological sciences. Timothy Dwight, while still a Professor in the Theological Department and before he had become a great President of Yale, pronounced the worth and unity in scholarship of all University disciplines including medicine. He extolled the benefits to be obtained from a full-time system in the medical school—that was then 40 years in the future. In that decade the Sheffield Scientific School began to function actively. In 1874, while an undergraduate just 18 years old, Russell H. Chittenden was chosen to be director of a laboratory of physiological chemistry, and in 1880 he received the first Ph.D. to be awarded in that subject in America. He had proceeded to educate himself in the laboratory of Professor Kühne in Germany, with whom he subsequently maintained a scientific collaboration, and in 1882 he was appointed Professor of Physiological Chemistry in the first great laboratory devoted to that science in this country.

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† Presented at the Sesquicentennial Anniversary Program of the Yale University School of Medicine.

It was in the first 20 years of the present century that two great deans transformed the Yale Medical School into a center of research. During the tenure of Dean George Blumer the interest of the University authorities was aroused so that, with the help of the General Education Board, the full-time system for clinical as well as basic sciences was introduced and an effective working relationship with the New Haven Hospital was established making clinical research possible. His dynamic successor Dean Winternitz, with the full support of President James Rowland Angell, was able to assemble a faculty of superb investigators and teachers while stimulating munificent donations from the Rockefeller Foundation, General Education Board, and Commonwealth Fund. The new donations made possible the construction of the first great plant of the school of medicine. Both deans were Hopkins trained. Thus, in the words of John Fulton, "the Hopkins discharged the debt it owed to Yale."

Professor Chittenden's laboratory was the intellectual birthplace of two others of the first great group of experimental biological scientists to teach at Yale, Profs. Lafayette B. Mendel and Yandell Henderson. These men were soon joined by Ross Granville Harrison, a Hopkins graduate, as Professor of Biology, and Harrison made discoveries of the first scientific magnitude. In providing proof that nerve fibers are an outgrowth of nerve cells he devised the method of tissue culture for animal cells. This method has ultimately led to such achievements as the development of the Salk vaccine. Professor Mendel continued in biochemistry at Yale pursuing the great tradition that has been maintained to the present day. Henderson acquired international stature as a physiologist as a result of his work on the physiology of respiration.

STUDIES OF THE "HIDDEN HUNGER"

With Chittenden, Mendel became one of the founders of the science of nutrition. The former had done pioneer work on enzymes in digestion, and considered as his greatest achievement the establishment of the protein requirements of man. Mendel, in collaboration with Dr. Thomas Burr Osborn of the Connecticut Agricultural Experiment Station, made the fundamental discovery that some proteins were nutritionally inadequate since they lacked amino acids that could not be synthesized by the body. These he christened "essential" amino acids. He was also a pioneer in this country in the discovery of vitamins, "substances which do not fulfill their physiological mission because of the energy which they supply." As early as 1910 he found an important growth factor in milk residue, which contained water soluble substances later known as "vitamin B." These were extensively

investigated by Dr. Cowgill. Three years later he discovered that a serious eye disease, xerophthalmia, developed in rats lacking the fat soluble vitamin A. Professor Underhill called attention to production in dogs of a pathological condition closely resembling human pellagra. Subsequent studies on vitamin deficiencies were conducted by Drs. Yudkin, Lambert, Tyson, and Smith. Important work on the effects of vitamin deficiencies on the nervous system was done by Dr. Harry Zimmerman and associates.

PROTEIN STRUCTURE

Recently knowledge of those remarkable biological catalysts, the enzymes, was notably advanced by the studies of proteinases by Professor Fruton and associates, and more specifically the discovery of transpeptidation whereby certain radicals can be replaced. This enzymatic mechanism explains in part the method whereby complex specific protein molecules can be created under physiological conditions by the elongation of peptide chains which are their building blocks. The first demonstration of the net biosynthesis of a discrete protein (cytochrome-C) in subcellular particles was by Dr. Simpson in 1958.

The means whereby the heart of the cell, the nucleus, is constructed has been under intensive investigation. Dr. Charles Carter's discovery that adenylosuccinic acid is an intermediate in nucleic acid metabolism is an important contribution. The structural basis of ribonuclease activity has been investigated by Dr. Richards. Dr. Welch and his active group have used chemically modified building blocks such as 5-iododeoxyuridine in the hope that these would be incorporated into nuclei, thereby impairing growth and possibly controlling tumors. At least partial success has been attained, thereby opening another front in the effort against neoplastic disease.

CHEMISTRY AT THE BEDSIDE

It has been asked: "What are thou life?" and answered: "A thing of watery salt held in suspension by a slime." At Yale the salt and water and the jelly of life have indeed been well studied. Brilliant work by Prof. Frank Pell Underhill during World War I brought out that both in war gas poisoning and in burns there were profound upsets in the water and salt metabolism of the body. Restoration of hydration and of salt balance produced a striking improvement. With the arrival of Dr. John Punnett Peters in New Haven, chemistry was more and more brought to the bedside. His masterpiece, the two-volume *Clinical chemistry* written with Dr. Donald D. VanSlyke, made the knowledge generally available. Dr. Peters became surrounded by eager and brilliant students who today comprise the Who's Who

of metabolic disease—Danowski, Epstein, Elkinton, Welt, and Max Miller, to mention but a few. Diabetes was shown to be, in fact, a state of starvation and that additional protein and sugar were needed to make up for the losses in that chronic disease. Later another sugar, fructose, was found to be better tolerated in this disease, as previously reported, and its study contributed knowledge of the nature of diabetes itself. In uncontrolled diabetes, diabetic acidosis, a state of shock was found to result from loss of salt and appropriate therapeutic measures were instituted. For many years Dr. Peters was the faithful head of a "Diabetic Acidosis Team" that day and night would attend these acute medical emergencies. The rapid intravenous glucose tolerance test for diabetes was introduced in the early forties and this has gained wide acceptance as a standard.

Fundamental additions to knowledge of carbohydrate metabolism were made in the late twenties and early thirties by Drs. Himwich and Nahum and associates. The glucose-lactic acid cycle involving muscle and liver were elucidated, and the respiratory quotients of many organs including brain were worked out.

The movement of water and salt within the body and its derangement in such other diseases as nephritis were an important preoccupation of the Peters group from which came noteworthy advances in the understanding and treatment of disease. Dr. Man, in collaboration with Dr. Peters and more recently with Dr. Margaret Albrink, has contributed to the study of blood lipids in diabetes, renal, thyroid, and other diseases. The problem of the blood fats has assumed a new interest in relation to coronary disease. Within the past three years a new era in the study of lipid metabolism was opened by Dr. S. R. Lipsky's adaptation of gas chromatography. Thanks to his work analytical micromethods for various fats are available and many critical separations can be accomplished for the first time.

In the Department of Pediatrics, a parallel effort has been directed at the metabolic problems peculiar to children by Dr. Daniel Darrow and such brilliant co-workers as Harold E. Harrison and Robert E. Cooke. Perhaps the most valuable and widely acknowledged contribution is the recognition that the loss of precious salts, especially potassium, from the body fluids, rather than the action of a toxin, is largely responsible for the profound consequences of diarrhea, especially in infants. Again replacement therapy proved the clue to success in treatment.

The presence of profound metabolic upsets in surgical patients has become increasingly apparent. Endocrine mechanisms, with special reference to thyroid-adrenal interrelationships, have been under investigation by Drs. Hayes and Goldenberg.

YALE AND HORMONES

The work of many investigators in several departments has made Yale an outstanding center of research on hormones. When Dr. Edgar Allen came to New Haven in the early thirties he brought with him from the University of Missouri an active group of younger men including Drs. Gardner, Diddle, and Burford, each of whom has gained distinction in his own right. Previous studies on the sex hormones were continued. They arrived at the estrogen-withdrawal hypothesis of menstruation which is now generally accepted. Estrogen, the female sex hormone prevents the onset of uterine bleeding; on withdrawal, menstruation is precipitated. Furthermore, this group found that these hormones possess the remarkable property of stimulating the growth of various organs and tissues, and of greatest interest, perhaps, that they could induce or otherwise affect the development of tumors. Drs. Hooker and Forbes made an important contribution in devising a test for one of these substances, progesterone.

Another substance, prolactin, concerned in the control of the secretion of milk, was prepared in highly purified crystalline form by Drs. White, Bonsnes, and Long. In 1940 Drs. Fry, Long, and Katzin demonstrated that adrenal steroids of the type of cortisone control the rate of gluconeogenesis, sugar formation from protein—an effect probably responsible for the therapeutic action of these agents in many types of disease. White and Dougherty made the interesting disclosure that cortisone reduced the number of circulating white blood cells—which led to the use of the substances in controlling certain forms of leukemia.

The first highly purified and potent preparations of ACTH, the pituitary hormone that acts as a whip to the adrenals, were isolated by Drs. Sayers, White, and Long in 1943. With these purified preparations it became possible for members of the group to show that this hormone specifically depletes the adrenal of cholesterol and ascorbic acid. This has been used throughout the world as a method for assaying ACTH or demonstrating its release in the body. In the years 1947-1950 Drs. Fry, Gershberg, McDermott, and Long demonstrated that epinephrine stimulated the release of ACTH. They were the first to point out that the secretion of ACTH was controlled by a dual mechanism, the first related to the activity of the hypothalamus and the second probably related to the level of adrenal steroids in the blood. These studies are being continued by Dr. Brodish. Another feat of purification of a highly important biological substance was that of Drs. Wilhelmi, Fishman, and Jane Russell who in 1948 succeeded for the first time in crystallizing growth hormone. Their method has now become the standard.

Shortly before coming to Yale, Dr. Lerner discovered that the pituitary contained a skin darkening hormone now known as melanocyte stimulating hormone (MSH). The chemical structure of hog alpha-MSH was determined by this able investigator and most of the chemical structure of human ACTH was established. Recently, a skin-lightening hormone, christened Melatonin effective in frog skin was discovered in pineal glands. To date, the political and social implications of the power to change the color of skin have been less thoroughly explored.

Another remarkable disclosure is from Drs. Bondy and Cohn, who state that unconjugated etiocholanelone, an adrenal hormone, is present in the blood plasma of individuals during attacks of a mysterious disease called periodic fever, a recurrent illness chiefly of Sephardic Jews.

The problems of the thyroid and of its iodine-containing hormone have long held the interest of investigators at Yale. The late Dr. William Salter was a pioneer in the development of chemical methods for the study of this hormone. He introduced the use of radioactive iodine, which is concentrated in the gland, as a means of reducing its activity for the treatment of congestive failure of the heart. Two widely used methods for the detection of biologically significant iodine in the blood have been worked out largely through the efforts of Dr. Evelyn Man. The first method for "protein bound iodine" (PBI) has been replaced by the more recently developed method for "butyl extractable iodine" (BEI). These techniques have served as tools for the investigation and scientific treatment of thyroid disease by Dr. Peters and his staff, first with Lugol's solution and later with the thiourea derivatives.

NORMAL AND ATYPICAL GROWTH

Aspects of growth, normal and abnormal, have been approached at the biological as well as at the basic chemical level. Dr. Samuel Clark Harvey, surgeon and philosopher, made fundamental contributions to knowledge of factors in wound healing, using the tensile strength of the wound for a quantitative approach.

The importance of tissue transplantation has just been acknowledged in the award of the Nobel prizes for 1960. Basic contributions to transplantation technique and theory have come from the laboratory of Dr. Harry S. N. Greene who disclosed that embryonic tissues and certain malignant tumors, especially those with the capacity to matastasize, can be transplanted to the anterior chamber of the eye or to the brain of another species, while benign neoplasms fail. Transplanted undifferentiated tumors sometimes reveal their true nature or origin in the new host. The method can also be used

for growing in the transplants, agents of disease specific for the donor but harmless to the host. These studies have great theoretical as well as practical importance. World-wide attention has been drawn to Dr. L. S. Stone's studies of returning or altered vision in transplanted eye of the salamander.

The community of science suffered a great loss in the recent death of Dr. Francisco Duran-Reynals, one of the most active champions and brilliant investigators of the virus theory of cancer. He demonstrated the infectivity of the Rous virus, a filtrable agent that can produce tumors in fowl, in duck embryos or newly hatched ducklings; mature ducks appear to be immune.

In animals of low resistance the Rous virus produced lesions like those of an infection, while animals with high resistance developed tumors. At the time of his death he was applying the fruits of another great discovery, that of a tissue-spreading factor, hyaluronidase, to his work with cancer. At the present time the role of viruses in various forms of cancer in animals is becoming increasingly apparent, and there are hints of their existence in some human tumors.

GENETICS

For many years strains of inbred mice, with relatively constant characteristics, were developed and maintained at Yale by Dr. Leonell Strong and his associates. These have provided a powerful tool for investigating many aspects of neoplastic and other diseases. They served also to replenish stocks lost in the fire at Bar Harbor whence the ancestors of some of these animals had come.

Outstanding studies in genetics have been done at Yale by Drs. Tatum and Bonner and their associates who demonstrated the transmissibility of specific enzymic characteristics in fungi, and by Dr. Lederberg who is credited with the discovery of sex in bacteria among his other contributions. The importance of this work was acknowledged in the award of the Nobel prize to several members of the group which was shared with Professor Beadle the teacher of some of them.

POWER OF THE INVISIBLE RAYS

Work on biological effects of x-rays at a fundamental level was done in the Department of Pathology by Drs. Hussey and Thompson as early as the twenties. The rate of radiochemical inactivation of enzymes was studied under various experimental circumstances. The influence of the rays on the development of Drosophila larvae was investigated.

At Yale Dr. John H. Lawrence, a brother of the physicist and Nobel Laureate E. O. Lawrence, pioneered radioactive phosphorus in the treatment

of diseases of the blood, especially leukemia. He and Dr. Robert Tennant were among the first to make a biological comparison of x-rays and neutrons in mammals. The study of the leukemogenic action of radiation in relation to genetic and other factors was begun in New Haven by Dr. Henry S. Kaplan and has been brilliantly continued in his present post at Stanford.

CONGEALMENT AND SOLUTION OF THE BLOOD

How much suffering and death we could prevent if we fully knew what causes the blood to clot! Here outstanding contributions have been made by Dr. J. Haskell Milstone in his analysis of the clotting mechanism into three separate stages. The purification of the substance thrombokinase, responsible for the initiation of the first stage, and subsequently its characterization as a trypsin-like enzyme, represent an important achievement.

Of great interest is the purification and characterization of an anti-clotting agent, plasmin, by Dr. D. L. Kline and colleagues. Its possible application in the solution of clots within living animals is being investigated by Drs. Hume, Glenn, and associates.

VASCULAR DISEASE

Diseases of the blood vessels now represent the most important cause of death in America. When Dr. Winternitz relinquished his deanship, he returned to an early interest in vascular disease. Almost at once he made the noteworthy discovery that hemorrhage within the walls of vessels contributes to the development of arteriosclerosis, and also to coronary occlusion. In this process the vessels of the vessels, the vasa vasorum, were shown to be important. The observations were summarized in a book with Drs. Thomas and LeCompte *The biology of arteriosclerosis.* The relation of the kidney to cardiovascular disease was explored in an extensive series of experiments. These considered differences in the lesions when both renal arteries were ligated, as compared with those following ablation of the kidney, and also the pathology produced by injection of renal extracts.

Dr. L. L. Waters found that a simple chemical compound, allylamine, produced remarkable lesions of the vessels, particularly coronary arteries of the dog and this has been extensively studied together with other factors, such as blood lipids in the pathogenesis of vascular disease.

ELECTRICITY OF THE BODY

That every living thing has about it an electrical field was a discovery of immense significance. In the hands of the Dutch physiologist, Einthoven, it found its first important application in the electrocardiograph. The mechan-

ism of the electrocardiogram has been illuminated by the work of Drs. Hoff, Nahum, and their associates. They disclosed the dominant role of the surface layers of the heart in determining the character of the electrocardiogram and helped to establish the quantitative contribution of the two chambers. A study of chemical influences revealed involvement of adrenalin in the effects of benzol and certain other substances, and the importance of acetylcholine in the genesis of auricular fibrillation. An outstanding contribution is to the understanding of the effects of electrolytes, particularly potassium. Further basic work by Dr. Nahum has contributed to the understanding of unipolar electrocardiography. Electrocardiography has been applied also to the study of fetal distress by Drs. Hon and Hess.

A wider investigation of the electricity of the body has been made by Dr. Harold Burr who has studied electrical fields related to various cyclical events such as ovulation, and the electrical correlates of growing cancer and even of growing plants.

STORMING THE BASTIONS OF THE BODY

One by one the formerly inaccessible fortresses of the body have been stormed. Access can now be readily obtained to the central nervous system, the contents of the chest, and even to the interior of the heart itself.

Free entry into the thorax was not possible until the development of technical methods, of which the most important was positive pressure anesthesia. To this both Drs. Joseph Marshall Flint and Herbert Thoms made a contribution. One of the most original discoveries in pulmonary physiology is that of collateral respiration—the demonstration of a "back door" to the distal air spaces—by Drs. van Allen and Lindskog. Dr. Lindskog also contributed the method of resection for lung abscess. Some of the earliest experimental observations on the collateral circulation were made by Dr. Schlaepfer in the twenties. More recently the expansion of the collateral circulation in disease, its effect on the shunting of blood, and its possible application as a means of building vascular bridges to the coronary arteries have been explored in a joint effort between Pathology and Surgery.

One of the first applications of surgery to cardiac problems was the development of pericardiolysis by Drs. Marvin and Harvey as early as 1924. By this technique the heart is freed from an adherent constricting thickened pericardial sac. An early cardiac pump was developed by Dr. William Sewell while still a medical student working with Dr. Glenn. Dr. Glenn devised also the ingenious procedure of sewing an artificial pouch to the heart through which structures in the interior can be approached and repaired. A major advance made by Drs. Glenn and Patiño is that of "right

heart bypass," a method of circumventing a deformed or incompetent right cardiac chamber by directly connecting the superior vena cava with the pulmonary artery. This method has now proved its usefulness in tricuspid stenosis and its utility in other conditions is under study.

Although man early in his history dared, by trephination, to enter the skull with therapeutic intent, the workings of its contents are still largely unknown. At Yale the functions of the frontal lobes have been explored by application of experimental brain surgery in higher apes, coupled with psychobiological training techniques. An outstanding achievement was the investigation of the effects of lobotomy by Drs. Fulton and Carlyle Jacobsen. As a result of this procedure, two anxious and temperamental chimpanzees, Becky and Lucy, were transformed to a commendable state of calmness and apparent rationality. This finding, reported at a Congress in London and also in Moscow in 1935, suggested a procedure for alleviating certain mental disorders in man, and this was first accomplished by Egas Moniz in Portugal. Dr. Fulton has been acclaimed the father of lobotomy, but he always modestly said that if he were the father, it was a case of unplanned parenthood.

The seat of the soul, if it is indeed in the brain, has not as yet been discovered, but the seat of a less noble property, the appetite, was discovered in New Haven. Dr. Brobeck, at various times in association with Drs. Tepperman and Delgado, found that injury to certain deeply lying centers in the hypothalamus led to an enormous increase in appetite, whereas injury to others nearby led to total anorexia. The psychological aspects of such changes in appetite have attracted the study of Dr. Neal Miller of the Department of Psychology.

That ancient portion of the brain which in higher forms is dominated and obscured by the greatly expanded cerebral cortex, has been brilliantly illuminated by Dr. Paul MacLean and his associates. He has called this limbic system the "visceral brain" to indicate its function as a major center for the correlation of every form of internal and external perception—what we "feel" as contrasted with what we "know". The latter function appears to be served by the outer mantle of the brain, the neopallium which reaches its highest development in man. The limbic system has been further explored by Delgado with the use of multiple electrodes through which stimulation or coagulation can be brought about. This system has been found to influence many phases of autonomic function such as the sexual, as well as patterns of emotional behavior. The limbic system has thus emerged as a distinct functional entity.

A method for stimulating portions of the brain in fully conscious animals by means of previously implanted electrodes was used as early as the thirties

by Dr. Richard Light of the Department of Surgery. In an extensive new development by Dr. Delgado it has been used not only in exploration of the limbic system but also in the study of the cerebral cortex in its various layers, as well as regions, and the work has been extended to man. At long last man's ancient interest in phrenology has been converted to a science.

MAN AND MIND

The idea so clearly conceived by Dr. Winternitz, that man is mind as well as body, and that he cannot be considered apart from the society in which he lives, led to the creation of the Institute of Human Relations and to the world-wide search for outstanding leaders in psychiatry. Numerous devoted efforts for the solution of problems falling into this sphere have been exerted but no more than a few can be mentioned: the dynamics of humor in relation to mental disorders (Drs. Levine, Redlich, Laffal, *et al.*); the interaction of the schizophrenic patient with his family (Dr. Lidz). Some extensive investigations have formed the basis of published volumes: *The initial interview in psychiatric practice* (Drs. Gill, Newman, Redlich, and Margaret Sommers) in the course of which recording techniques were developed and extensively applied; *Social class and mental illness,* an interdisciplinary study by Profs. Hollinshead and Redlich. Psychological studies of lobectomized patients have been made by Dr. Brody.

The inseparability of mind and matter has been recognized: Dr. Daniel Freedman, after training at the National Institutes of Health, has established a laboratory of Psychopharmacology in collaboration with Dr. Giarman, Professor of Pharmacology. Drs. MacLean and Delgado have held joint appointments with physiology.

It was in the hope of obtaining a better understanding of man, that primate biology and psychobiology were extensively developed by Dr. Robert M. Yerkes in the colonies at New Haven and at Orange Park, Florida. Such topics as intelligence, comparative psychology and psychopathology, social behavior, mother-infant relationships, received special attention, especially in anthropoids. Opportunities were also seized for investigating the somatic sphere such as the chromosomes and reproductive cycles. Two classic volumes were published: "The Great Apes" (1929) and "Chimpanzees" (1944). New interest is manifest now in the support of several "primate centers" in this country by the Public Health Service.

CARE OF MOTHER AND CHILD

The poet said "The child is father of the man." Nowhere in this country has the understanding of the mother and of the physical and mental nurture

of the child been better served than at Yale. Dr. Thoms' new method of x-ray pelvimetry made possible the accurate measurement and classification of that "graceful arch 'neath which the noblest heads have passed." Under Dr. Donald Barron there have flourished studies of prenatal life which he had begun at Cambridge as a student, and later collaborator of Barcroft. Dr. Barron's recent researches have contributed to the elucidation of how oxygen, the breath of life, and other nutrients are transferred across the placenta and how these are used in the growth of the fetus. In this work various barriers have been broken. His associates have come from other Departments and even from other Universities, Boston, Harvard, and Johns Hopkins. Recently this work has brought him and his associates to the peaks of the Andes where the problems of the fetus are immensely magnified by the rarified atmosphere.

In her intensive observations over a long period of years Dr. Gertrude van Wagenen has provided valuable data on the sexual cycles, response to hormones, gestation and birth in a primate species, the macaque.

Dr. Edward Hon combined his expert knowledge of obstetrics and electronics to develop with Dr. Orvan Hess, an early warning method to detect fetal distress. One principle early employed by them was to record the fetal electrocardiogram apart from that of the mother and to subtract by electronic means the latter from that of the fetus. More recently the procedure has been simplified.

The Read method of "natural childbirth" was introduced into this country at the New Haven Hospital largely through the influence of Dr. Herbert Thoms and "rooming-in" was born in New Haven. This scheme of caring for the mother and her newborn infant together in the same unit of space, was initiated through the interest of Drs. Powers in Pediatrics, Morse and Thoms in Obstetrics, and Dr. Edith Banfield Jackson who directed the project with such able assistants as Drs. Olmstead and Ethylyn Klatskin. The cooperation of the administrative staff of the hospital was granted, with some misgivings, by Dr. Snoke. The term rooming-in came into general use with its theoretical description in the book *Infant and child in the culture of today* by Drs. Gesell and Ilg. The "rooming-in" principle is now widely used in many institutions.

The principles of infant nutrition were clarified by Dr. Grover Powers and his group who emphasized the total caloric intake of a suitable mixture of proteins, fats, and carbohydrates, with vitamin supplement. A successful regimen for premature infants was worked out which has been of incalculable benefit. The massive problem of rickets was attacked and the importance of sunlight in its prophylaxis and therapy was demonstrated. Studies

of vitamins also were a long and important preoccupation of the Pediatric Clinic.

The Yale Clinic of Child Development has exerted a profound influence on the life of the civilized world. From its modest beginnings in 1911, it came to full bloom in the early thirties in its magnificent quarters in the Sterling Hall of Medicine. "Gesell" became a household word as volume after volume appeared describing the norms of development as observed by painstaking cinematographic and other methods by Dr. Gesell and his associates, Drs. Thompson, Amatruda, Ilg, Ames, and others.

Those who have brought up children "according to Spock" also have not escaped a touch of the Yale spirit since this eminent pediatrician received his medical degree in this city.

New approaches have been made under Doctor M. J. E. Senn, the present Director of the Clinic, who has emphasized the understanding of the child within the background of his family.

BATTLE OF THE MICROBES

In the struggle against pestilence, men of Yale have struck valiant blows. Dr. Francis Blake who had been brought to New Haven by Dean Winternitz as Professor of Medicine, had been a member of the Army Pneumonia Commission during World War I, and had worked for an additional 20 months of post-war service at the Army Medical School in company with Dr. Russell L. Cecil. Together they produced a series of classical papers on the pathogenesis of pneumonia. With this experience behind him, his interest in the disease was maintained and he, in collaboration with Dr. James D. Trask, made early disclosures on the development of variants of the pneumococcus, particularly the production of the "rough" unencapsulated form by growing the "smooth" forms in immune serum. Another contribution was the introduction of pneumothorax to relieve discomfort and dyspnea in the acute phases of the disease.

In the 1920's scarlet fever was a dread disease with a high mortality. Following the discovery by Dochez that the disease was caused by a toxigenic hemolytic streptococcus, the toxin was demonstrated in the blood and urine of patients. Drs. Blake and Trask moreover were able to show the effectiveness of an antitoxic serum.

Concurrently another disease thought to be of streptococcal origin, rheumatic fever, was being intensively investigated by Dr. John R. Paul. The spread of the disease was studied within families as a clue to the more general problem of its transmission. Such "family epidemiology" he applied subsequently with notable success in the study of poliomyelitis, and it has

been widely used by others in the investigation of infectious disease. What is now known as the Paul-Bunnell test for infectious mononucleosis was in fact a by-product of these studies—an example of serendipity which in Dr. Greene's paraphrase is the "finding of farmers' daughters while searching for a needle in the haystack." There seemed to be some similarities between rheumatic fever and the serum sickness which followed the administration of horse serum then being used extensively in therapy. It had been discovered that the plasma of persons with serum sickness had the remarkable property of causing the red blood corpuscles of a foreign species such as the sheep to agglutinate—as if the person had been previously injected with them. Substances responsible for this phenomenon were called heterophile antibodies. This led Dr. Paul and his associate Dr. Bunnell to investigate the blood of persons with rheumatic fever together with "controls" suffering from a large variety of other conditions, for such antibodies. It was found that individuals of the "control group" with infectious mononucleosis had the highest concentration of antibodies and this has subsequently been used as a test for the disease. As a historical aside it is interesting that the first patient in the series was a medical student who is now the Connecticut State Commissioner of Health.

In 1931 the Yale Poliomyelitis Unit was founded. From its beginning with the collaboration of Drs. Trask and Paul it has been carrying on outstanding work to this day. No less than 6 of the 17 members of the "Polio Hall of Fame" have at one time or another worked in the Unit. An immediate contribution resulting from the application of the technique of "family epidemiology," was the demonstration of virus in the throats of persons with nonparalytic disease during epidemics of the paralytic form. Within two years it was disclosed that there was more than one type of polio virus. Of major importance in understanding the dissemination of the disease was the discovery of the virus in intestinal contents of patients, in sewage at the time of greatest prevalence of the disease, and in flies obtained from the near vicinity of houses harboring infected persons. Remarkable investigations in what may be called "serological epidemiology" were begun in 1943 when poliomyelitis was found to occur frequently in soldiers in North Africa. It was then observed that practically all adult natives in this region carried antibodies in the blood—having apparently been immunized much earlier in life in consequence of the great prevalence of the infectious agent. Paradoxically, high standards of cleanliness appear to decrease the immunity of a population. This is a general principle of epidemiology in the tropics, that has been demonstrated with reference to diphtheria as well as to poliomyelitis: crowding and filthy conditions of life make for universal infection

and only those that acquire immunity survive. The presence of immune bodies could also be used to establish the occurrence of infection in years past, as was demonstrated among the Eskimos in such regions as Point Barrow, Alaska. In the 1940's came the discovery of the Coxsackie group of viruses. Subsequently Dr. Melnick and his collaborators in the Unit were in the forefront in classifying this large family of agents and in studying the diseases produced by them. In 1950 Dr. Dorothy Horstmann demonstrated poliomyelitis virus in the blood early in this disease, thereby illuminating its method of spread through the body, a fact established almost simultaneously by Dr. Bodian at Johns Hopkins. In the 30 years of the existence of the Poliomyelitis Study Unit more than 325 papers have been published, an indication of the activity of this group. Currently, work is progressing apace in the study of the live poliomyelitis vaccines.

As early as the nineteen twenties hepatitis was a subject of study in New Haven. It was then that Dr. George Blumer wrote of his conviction that catarrhal jaundice was a sporadic form of epidemic hepatitis, but this was not generally accepted for 20 years. During World War II Dr. Paul Havens then at work in New Haven made important contributions to the differentiation of infectious hepatitis and serum hepatitis, a clinically similar disease transmitted by contact with infected blood as in transfusions, or even by needle punctures. He also demonstrated that infectious hepatitis could be transferred from man to man by feeding the virus. In the hands of Dr. Gerald Klatskin the liver biopsy method has yielded significant information on the natural history of hepatitis and of granulomatous and other diseases of the liver.

Infections of the kidney, pyelonephritis, were studied by Dr. John Peters and Dr. Zimmerman who emphasized the frequency of the condition in pregnancy and its relation to the subsequent development of high blood pressure. Within the past few years noteworthy contributions to the study of this disease have been made by Dr. Paul Beeson and his associates, chiefly Drs. Lawrence Freedman, Rocha, and Guzé. They have concerned themselves with the peculiar susceptibility of the kidney to infection with coliform bacilli. While on a working sabbatical in England, Dr. Beeson with Dr. Rowley reported that kidney tissue interferes with the bactericidal action of blood serum for these organisms. This activity is 5-15 times greater than that of other tissues, and is exerted on the fourth component of complement, that which is characterized by susceptibility to injury by ammonia. Phosphate and glutamine which favor ammonia formation, enhance the anticomplementary activity of renal homogenates.

Infection with a new species of Listerella was reported by Dr. C. G. Burn.

Serious attention has been paid to the important subject of the bacterial toxins. The most highly purified preparation of diphtheria toxin available to that time was prepared by Drs. Bayne-Jones and Eaton and its properties revealed. The spread of tetanus toxin along nerves in the pathogenesis of tetanus was also investigated by the former. Immunity in tetanus, with special reference to the toxoid, was studied by Dr. P. B. Cowles.

The economy of state and country was handsomely served by another bacteriologist, Dr. Leo F. Rettger, through his work on the destructive Salmonella-induced diarrhea of chickens, and on infectious abortion in cattle. He contributed also new information on the intestinal flora especially on the effects of the *Lactobacillus acidophilus.*

In February, 1944, Yale University was presented with a collection of over 300 chemical products that had been isolated from the tubercle bacillus. This, the work of Dr. Rudolph J. Anderson and his associates, represents the most complete chemical dissection of an organism ever made. It was begun in 1926 when Dr. Anderson came to Yale at the invitation of Professor Treat B. Johnson, who had already been working with nucleic acids and proteins of this species. The effects of many of these substances in animals were studied by Dr. Florence R. Sabin at the Rockefeller Institute. Dr. Anderson's work was one of the first demonstrations of the value of long term grants, in this case from the National Tuberculosis Association.

With the new era of effective chemotherapy in infectious disease there arose new opportunities and problems. Dr. Francis Blake with such associates as Hageman, Haviland and Sadusk were able to make significant contributions regarding the absorption, excretion, dangers and most effective clinical use of the sulfonamides. In June of 1941 Dr. Francis Blake had an earnest conversation with Prof. Howard Florey and six months later gave the first dose of penicillin in this country to a patient with post-abortal streptococcal infection from which she then miraculously recovered. Dr. Beeson and his staff have carried forward this tradition of intensive study of chemotherapeutic agents and have joined with Dr. Welch in planning a special unit for the intensive study of these substances in infectious disease, cancer and other conditions.

ANIMAL HEAT

Fever is a frequent accompaniment of infectious and some other diseases and the effects of substances which control it, the antipyretics, have been of interest to physicians throughout the ages. Significant physiological studies were done by Dr. Barbour who demonstrated the importance of water transfer, and of the nervous system in the control of cutaneous circulation. More

recently Drs. Beeson and Ivan Bennett have investigated the properties of pyrogens in bacteria. They have also found a pyrogenic material in white blood cells. Dr. Elisha Atkins, pursuing another facet made the important disclosure that pyrogens, made by the body, can appear secondarily after injection of exogenous pyrogens such as bacteria or even certain viruses. The role of etiocholanelone in "periodic fever" has already been mentioned.

HEALTH OF THE PEOPLE

There has been a great tradition in Public Health at Yale succinctly phrased in Professor Winslow's credo: "Within natural limitations a community can determine its own death rate." Work toward this end consisted, in part, in the development of standards for health organizations. Techniques of community health surveys were developed, an activity in which Professor Hiscock played a large and direct role. Such cities as Boston, Pittsburgh, Cleveland, Minneapolis, Kansas City, San Francisco, and Los Angeles were actually surveyed. The standards established have been almost universally accepted as the basis for community health programs. Studies in industrial hygiene begun by Dr. Leonard Greenburg have been continued by Dr. Wister Meigs who has investigated such industrial problems as that of carbon monoxide poisoning. In the J. B. Pierce Laboratory of Hygiene, fundamental physical and physiological studies of the relation of environment to comfort and survival have been made. Socioeconomic factors in cancer have been extensively investigated by Dr. Cohart. The abiding interest of the Department in more local affairs has been expressed in housing within New Haven and in the founding and support of the Connecticut State Department of Health.

DENTAL RESEARCH AT YALE

Although there has never been a school of dentistry at Yale, there has been much interest in dental research fostered especially by Dr. M. C. Winternitz and led for many years by Dr. Bert G. Anderson. During its most active years, in the middle thirties, the Dental Research Unit was supported largely by the Rockefeller Foundation and obtained its recruits from among outstanding graduates of dental schools who then took additional work at Yale towards the M.D. degree, while participating actively in investigative work. Collaboration and supervision were obtained from men in several departments of the School of Medicine, among whom Dr. C. G. Burn was most active. The accomplishments of this group were solid. Dental caries, periapical infection, the role of hypersensitivity in localizing infection, enamel formation, and changes in congenital syphilis

and from excess of fluoride, were among the many subjects of study. Remarkable adamantinomatoid proliferations were discovered in animals with vitamin A deficiency. Many of the men trained in this unit have gone on to positions of leadership in dental education and research elsewhere.

YALE MEDICINE IN WARTIME

In time of war a great University and a great Medical School may be assets more valuable to a nation than an army or fleet. In those times of stress Yale has abundantly given of herself both at home, and closer to the battle. It is to be expected that senior professors should be called upon to direct such affairs as those of the National Research Council, as was Professor Ross Harrison in World War II; of the Army Epidemiological Board as was Dr. Francis Blake; and of the medical work of the Chemical Warfare Service as was Dr. Winternitz. These represent a very few of the many services thus rendered.

In World War I Dr. Winternitz, as well as Dr. Underhill, had much to do with the investigation of the biological effects of war gases, and he published a classical monograph on the subject. When the first World War ended, the CWS laboratories were flourishing, but when World War II began he complained that all he found was a "desiccated kernel." From this humble beginning came the medical laboratories of the Army Chemical Center at the Edgewood Arsenal. An important result for civilian medicine was the discovery by Dr. Alfred Z. Gilman and associates that the nitrogen mustards could inhibit the multiplication of cells. This has found application in the treatment of cancers and leukemias.

Yale has been closely associated with aeromedical research from its beginnings. Early in the century Professor Yandell Henderson engaged in high altitude investigations with particular reference to anoxia, and during that war he became the Chairman of the first Committee on Aviation Medicine to be formed in this country. In the course of World War II a large decompression chamber was installed at the Sterling Hall of Medicine. Here were done important studies on anoxia, shock, and adrenal mechanisms. Outstanding contributions in the Yale Aeromedical Unit were those of Dr. Walter Miles of the red dark adaptation goggle, and of a practical G-suit by Dr. Lamport. Both items received important applications in action.

In both World Wars hospital units were organized at Yale, each time designated "The 39th." In World War I a major contribution was that of the Mobile Surgical Unit, a concept brought to our Army for the first time by Dr. Flint, who had previously studied it intensively among the French. This led to the development of mobile units of all types in World War II. In

the Second World War the Yale Unit in the Pacific contributed the discovery that the widely prevalent and disabling form of "jungle-rot" was in fact caused by diphtheria bacilli, which then produced epidemics of the common throat disease among susceptible soldiers. Natives of the tropics except for a brief period between nine months and two years, were found to be immune, again demonstrating the general epidemiological principle of immunity in the tropics that was well studied in relation to poliomyelitis. The epidemiology and natural history of hookworm disease were also investigated. A species of diphtheria-like bacillus hitherto undescribed also was discovered as a common organism in the respiratory tracts and skin infections of men in the tropics.

The investigation of the atomic bomb casualties in Japan was led by the late Dr. A. W. Oughterson, who had been Surgical Consultant to General MacArthur. Four of the seven Medical Officers who carried out the study at Hiroshima had been members of the Yale Unit, or had received their medical degrees in New Haven. Their work, published as a monograph, represents the only definitive report of the subject.

It may be asked what is the place of research in an institution that is a *school* of medicine. Surely the concept of the "trade school" dissolves as it becomes more widely understood that the quality of the scholarship needed to learn how a cell grows in the milieu of the living body, may not be less than that required to annotate creatively the papers of a great man in the framework of his time. Surely the natural home of scholarship in medicine is the university which leavens it, and which is in turn leavened. No physician is better than his science and his humanity, and his science is no better than the research which gives it nourishment. A school devoted to research is preoccupied with the process of *learning*—a preoccupation which after all means the best teaching. At this school every student must have an experience in research before the degree Doctor of Medicine is awarded. Research at Yale is an attitude of mind that precludes the cessation of learning—a continuing adventure in which the young may join older colleagues in the exploration of the unknown and in the hopes of achieving, in the clinic as in the laboratory, an ever improving understanding of man and nature.

A documented account, hopefully worthier of the subject and with fewer omissions of important work, will be published as a chapter in the Sesquicentennial Commemorative Volume.

SIR HOWARD FLOREY*

Department of Pathology, University of Oxford, England

MEDICAL SCIENCE IN THE TWENTIETH CENTURY†

I deem it a signal honour to have been asked to give this address during the celebration of the one hundred and fiftieth anniversary of your renowned Medical School, particularly as such emphasis is being given in your ceremonies to historical matters for, as you know, I have no claim whatever to be considered a medical historian. My only qualifications to talk on this matter are that I have spent nearly half of this century doing some sort of research related to medicine, and that I can claim to have great sympathy with those who study history, for I believe that some background of medical history is helpful in giving depth to current thought and that it is of great benefit to the student to know more than the bare bones of his subject.

It is no doubt salutary to consider from time to time what our ancestors have done in their day and to examine the achievements of the present in the light of the past, for there is and perhaps always has been a tendency, especially among the young, to believe that all current knowledge was acquired in the last ten years or so. Such an examination is particularly relevant in this University for you are the proud possessors of one of the greatest of the medical historical libraries of the present day, and this no doubt colours thought in your Medical School. It is a great grief to us all that the man‡ who played so outstanding a part in the building up of this fine library, and who was the repository of so much learning freely put at the disposal of others, is not with us today. But we all think of him with affection and I am sure his work for your School will be valued and remembered for as long as this Library lasts.

It is clear that the current of medical thought did not make any perceptible deviation from its course because the calendar suddenly changed from registering 1899 to registering 1900. We cannot therefore consider twentieth century medicine completely divorced from what had gone before, particularly in the nineteenth century.

The great base on which the medical and surgical practice of the nineteenth century had been elaborated was laid by the careful correlation of the

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† Presented for the Sesquicentennial Anniversary Program of the Yale University School of Medicine

‡ John Farquhar Fulton (1899-1960) Sterling Professor of Physiology 1930-1951, Sterling Professor of the History of Medicine 1951-1960.

symptoms and signs associated with illness in the living patient with the pathological changes that could be observed in the post-mortem room.

At this distance in time we can perceive that a great development of experimental science, not confined to any one branch of learning, was well under way in the nineteenth century. The pace of development has greatly accelerated in the twentieth century but the general lines that that development has followed were laid in the nineteenth.

At the same time as this growth of experimental science was taking place there occurred a steady accumulation of knowledge based on the accurate observation of patients alive and dead. From both observational and experimental sources the contributions to knowledge that had been made by the end of the nineteenth century were indeed formidable in their extent. Particularly striking were the advances in surgery which, starting with the introduction of anaesthesia and then of antiseptic surgery, had culminated in the production of a technique on which all twentieth century surgery is based, and which was incomparably in advance of anything that had been thought of in all previous time, at least as far as we know it.

At the beginning of the twentieth century the great currents of clinical observation and experimental investigation were beginning to fuse, and some influence was being exerted on the outlook of those who proclaimed somewhat loudly that medicine was an art and would never be a science. Even today we still hear the echoes of these sentiments, but none I think would deny that the advances in knowledge due to scientific investigation initiated in the nineteenth century are now having a tremendous impact on the practice of both medicine and surgery.

Thus it can be said that at the turn of the century the experimental approach to all problems associated with medicine was rapidly gaining momentum and that what we have witnessed since then is principally characterized by the expansion of the scope and complexity of experimental methods, not only in the laboratory but also in the clinic.

CELLULAR THEORY

Let us now turn to some specific examples of what I have just said. I suppose that the cell theory could reasonably be considered one of the most fruitful biological hypotheses that has ever been proposed. The idea that the cell was a unit of living matter led to a searching analysis of both normal and abnormal appearances of cells, so that by the end of the nineteenth century a great deal was known about their general structure and behaviour. By that time these studies had led on to practical uses in medicine, for methods had been sufficiently perfected and enough knowledge had accumulated to make

histological examination of pathological lesions an increasingly important element in the practice of clinical medicine.

Workers of the twentieth century, at first by methods which were essentially those of the nineteenth century and then by methods which are the prerogative of this, have pursued the great problems of cellular organization.

It was an important step forward when, by means of phase contrast and other variants of ordinary light microscopy, it became possible to view in cells in the living state many of the finer structural details not previously clearly observable in such conditions. This was of importance not only because of what could be seen in living cells but because it was shown that the picture obtained from fixed cells was not necessarily a gross distortion of the appearance of living cells.

Phase contrast microscopy was the invention of physicists, and at the present time our indebtedness to physicists and electronic engineers grows ever greater, because the production by the Germans of the electron microscope and the elaboration of methods, chiefly in the U.S.A., for its use in examining biological materials has ushered in what appears to be a new era of morphological studies.

This great new outburst of interest in the structure of cells, deriving from the extraordinary resolving power of the electron microscope, has come at a fortunate time, for it coincides with the development of biochemistry into a discipline which pervades all branches of medical investigation and largely conditions our thoughts on every medical problem, not excluding psychiatry.

RISE OF BIOCHEMISTRY

It would be very short-sighted indeed to imagine that our nineteenth century forebears had not discovered some very important and fundamental facts about the way in which living systems work, but the great advances of physics and of organic and physical chemistry which characterize this century enabled chemists to demonstrate that the hitherto seemingly daunting complexity of living matter may not be beyond elucidation in molecular and atomic terms. For example, the structure of molecules as large as that of myohaemoglobin has been unravelled by chemists and X-ray crystallographers. The problem of how protein molecules are continuously formed in the cell is yielding to analysis by current methods. In this connection the importance of the nucleic acids is now recognized and one of the triumphs of recent research is the elucidation of the immensely complicated structure of desoxyribonucleic acid—which is now thought to be intimately concerned in the mechanisms of heredity.

During this century biochemists have built up an extensive knowledge of the interplay of many of the enzyme systems of the cell largely from the examination of tissue slices and somewhat crudely mashed-up cellular debris. Methods are now becoming more subtle and attempts are being made to locate the enzyme systems, which are already known to exist, in certain cell components that are clearly displayed by electron microscopy. Thus cytology and biochemistry are going hand in hand in the elucidation of the fundamental properties of cells.

ISOTOPES

The dependence of medical science on advances in physical and chemical science is nowhere better illustrated than by the present-day use of radioactive isotopes. Isotopes of many of the elements for use in biology and medicine can now, as it were, be bought over the counter, but the research underlying their production embraces much of modern atomic physics. Certain radioactive isotopes, which are used as labels, are indispensable for the biochemical analysis of complex processes. This use of the most subtle "tracers" in biological and medical research has a history of only 20 years.

But I can hear you objecting that what I am talking about is general biology and not medical science. I take the view, which is amply supported by all historical evidence, that the practice of medicine will depend in the future as much as it does at present on a foundation of knowledge of the functioning of the units which make up the body. Who can doubt that with the intensification of the search for an understanding of the intimate mechanisms of the cell—a search which is going very well at the present time—we may for example eventually obtain a real understanding of the changes that occur when cells become cancerous?

However, the elucidation of the mechanism of the cell in the somewhat restricted sense that I am considering is only one of the fields in which biochemistry and physiology have played such an important part in this century. Clearly I can do no more than pick out one or two examples of what I mean by this.

THE VITAMINS AND HORMONES

A good illustration is afforded by the vitamins. The existence of such substances was discovered by observations on human beings. People who suffered from beri-beri were cured by the addition of rice polishings to their diet. This observation was amplified by biochemists to such good effect that now there is a great array of vitamins the functions of which are known in a broad way. The structure of many of them has been elucidated and some

have been synthesized. Truly a monumental performance for a short 50 to 60 years.

The hormones give another example of the same spectacular progress. They were first detected by observations in the clinic on man, and indeed the first successful therapeutic use of a hormone was the treatment of thyroid deficiency by dried thyroid gland long before it was known what the essential material in the thyroid gland was. Within this century a large number of hormones from the ductless glands have been not only isolated, crystallized, and their functions defined, but many have been synthesized including some that are very complicated, as they are polypeptides.

It is hardly necessary for me to say to an audience such as this what the effect of the physiologists' and chemists' work on these substances has been on the practice of medicine. We must not suppose that this work has come to an end; it is at the present time in full flood, and we can look forward to ever-increasing knowledge about the mode of action and properties of these very remarkable groups of substances.

It appears now that there is scarcely a single problem associated with disease which will not sooner or later be stated in biophysical and biochemical terms, so I regard the rise of biochemistry, allied with physiological experiment, as one of the most striking events in medical science in this century.

IMMUNOLOGY

An arresting feature of twentieth century medicine is the decline in the number of deaths from infectious disease, especially in the younger age groups. Much had been done in the nineteenth century towards achieving this decline by public health measures, and to this has been added the study of immune processes which has led to many important practical results. The success of immunization against diphtheria serves as an example. This started by the recognition of diphtheria toxin in the nineteenth century and the discovery in this century that the toxin can be rendered harmless by formalin without losing its immunizing properties. Toxoid is used for immunizing children in the United States, so that now practically all your young medical men have never seen a case of diphtheria. The rarity of tetanus in the last war was due to immunization based on the same discovery with tetanus toxin.

Other immunization procedures are of great practical importance, and immunological studies are still being pursued with the utmost vigour. That a branch of study can be known as immunochemistry further illustrates the penetration of chemical ideas into a complex biological field.

Interest is now moving to the study of tissue immunity. Why does a host reject a graft from another animal of the same species? It seems clear that immunity reactions are involved, and it is possible that the study of these may give sufficient knowledge to enable homografting to be undertaken. Such an alluring possibility for the surgeon awaits the results of laboratory investigations.

VIRUSES

Although chemists are now indispensable in many branches of medical research, it must be pointed out that they are still sometimes dependent on those who understand aspects of the behaviour of cells other than the chemical. A good example of what I mean is furnished by the study of the filterable viruses, which is now a growing and exciting branch of science that was unknown 50 years ago. The viruses were discovered by a botanist, as it happens, in the first instance. By now it is not only known that many human and animal infections are caused by such agents, but methods for their cultivation have been worked out and applied on a large scale. The very distinguished zoologist Ross Harrison, who worked for so long at Yale, could scarcely have foreseen, when at the beginning of this century he started cultivating the central nervous system of frogs in drops of plasma, that elaboration of his experiments would enable the virus of poliomyelitis to be grown in sufficient quantity to provide both dead and live vaccines, such as may go a long way to control the disease. The techniques used by virologists are among the most elegant and exacting in use by biologists at the present time.

Just to keep our feet on the ground I might point out in parenthesis that the initial work on vaccination against smallpox was all carried out on man in the eighteenth century. To be sure there were some casualties but nonetheless that immunization may still be considered one of the greatest applications of knowledge of virus behaviour to practical medicine.

HYGIENE

I should not wish to leave the impression that all medical advances are due to elaborate technical procedures. The great public health measures to which we owe our clean water supplies and the admirable sewage arrangements which characterize even the smallest towns in these days were due to nineteenth century reformers who started their great work before the recognition of the importance of bacteria, but whose efforts to make communities clean nevertheless led to a spectacular diminution in the frequency of intestinal and other diseases.

The incidence of, and the death rate from, tuberculosis was steadily falling throughout the latter half of the nineteenth century. This fall was not due to any specific methods of treatment but rather to the application of what was then known as hygiene.

CHEMOTHERAPY

The twentieth century can rightly claim to be the century of successful chemotherapy against infectious diseases, although it should not be forgotten that that very important chemotherapeutic drug quinine was discovered by primitive people in South America long before the Spainiards came there in the sixteenth century. It was at the beginning of this century that deliberate efforts were made to elaborate chemical compounds which would be more toxic to infective agents than to the host which harboured them. An early discovery was that atoxyl, an arsenic compound, cured mice infected with trypanosomes. Attention was then turned to the possibility of elaborating arsenic compounds which would be effective in treating syphilis by acting against the spirochaete which causes it. Salvarsan was the result of this research. Although it was introduced for the treatment of syphilis at the beginning of the century, we had to wait until the 1930's before any chemical compounds appeared which were capable of dealing with infections caused by bacteria. The discovery first of Prontosil and then of the whole family of the sulphonamides was due to what would now be called a survey. Chemical compounds produced by one of the great dye companies in Germany were screened for their action on infection induced in mice by the intraperitoneal injection of streptococci. These experiments were particularly important as they were designed to test the effect of antibacterial substances in the animal and not in a tube, as had so often previously been the case. By relatively simple experiments carefully and tenaciously carried out in the laboratory during many years, the almost miraculous properties of the sulphonamides were discovered. After work on animals they were tested in man and although the results at first were received with some scepticism and their wide introduction to medicine was relatively slow, their discovery was what is now known in every-day jargon as a "break-through."

The recognition of the therapeutic capacity of some antibiotics did not rest on any new discovery but on chance observations and the application of well-known and relatively simple experimental methods. The phenomenon of antibiosis and the chemical basis on which it rested has been repeatedly recognized since the 1880's. Indeed, attempts were made to use some antibiotics, notably pyocyanase, for clinical purposes at the beginning of this century. Chemical methods, in particular those suitable for dealing with

labile biological materials, have been greatly improved since then, but the manipulations by which penicillin was separated in the first instance were not novel, nor were the biological experiments of a new type. Let me be quite clear. Some antibiotics are novel in the sense that their differential toxicity, as between bacterium and host, is very great, but the introduction of antibiotics into practical medicine did not either stem from or result in the enunciation of any new principles affecting medicine.

The somewhat accidental nature of the discovery of the effects of antibiotics has influenced the direction of certain current researches. Enormous surveys are now being made of fungal products and other chemicals in the hope that something will turn up with a differential toxicity for normal and neoplastic tissue. Whether anything of real value will be found by the use of such blunderbuss methods remains to be seen, but the odds against it seem rather long. The nature of a problem must be very intractable to warrant such blind surveys but they are certainly one method, if resources are great enough, which can be followed in the hope that something may turn up.

PHARMACOLOGY AND THE DRUG INDUSTRY

But once a lead is obtained, the possibilities are immense, for one of the striking phenomena of the twentieth century is the growth of the pharmaceutical industry, the research facilities of which are largely devoted to exploiting the increasing knowledge of pharmacologically active substances. When I first started studying medicine, there were few drugs that actually did anything—one had a few powerful alkaloids, digitalis, the salicylates, some anaesthetic agents, adrenalin, dried thyroid gland, purges and the like. Now the medical man has at his command numerous drugs of great potency for good (and sometimes for ill), thanks to the combined activities of pharmacologists and chemists.

Evidence for their activities is seen in the many glossy advertisements in medical journals and in the heap of paper that arrives by almost every mail on the desk of all medical people. Often free samples are given away to tempt practitioners to try the various competing drugs. I expect we all find some useful to give away to friends even if we don't take them ourselves. But the great production of potent drugs, often with similar actions, raises many problems for those practising medicine, not the least being how to deal with patients who read *Time* magazine or *The Reader's Digest*.

It may be that a social historian of the future will find pertinent material in these advertisements. He would for example be struck by the number of drugs which are said to stimulate our central nervous systems and the number that will tranquillize us. He might deduce that life is more wearing now

than it was; but is it? Perhaps it is only that the pharmaceutical industry is busier than it was. But however exaggerated some contemporary manifestations may be, there is no doubt that the medical man is now furnished with many powerful weapons which are of great benefit in combating disease.

PSYCHIATRY

The twentieth century has seen a revolution in the conception of how man's mind works, and in particular it has seen the discovery of the importance of the subconscious mind. There have followed revolutionary attempts to deal with mental patients. Keen observation and relentless analysis of the behaviour of man himself has been responsible for this and it could hardly have been otherwise. No one doubts the immense importance of the study of psychology and psychiatry, no one can deny the immense increase in understanding of the mind acquired during the last 50 years, and yet one senses among those who are not psychologists or psychiatrists some misgivings about the present-day position. There is an apparent lack of precision in the study of the mind that some find baffling after considering, shall we say, the chemistry of the hormones. No doubt this attitude is in some ways unfair, but some think that a step forward in the understanding of many mental aberrations will result from the introduction of more biochemical and genetical thinking into psychiatric investigation.

Some consider that the study of genetics in relation to human disease has not been pursued as it should have been. This is, perhaps, because it is fantastically difficult to work with such a genetically heterogeneous population as man, but one of the interesting current developments is the investigation of congenital anomalies in terms of the chromosome, and contemporary medical journals bear witness to the fact that the study of cytology as practised by zoologists may throw light on some obscure inherited conditions in man.

CLINICAL RESEARCH

We hear—at least in Great Britain—a good deal about the needs of "clinical research," as if some particular mystique were associated with it. I sometimes wonder whether the present-day exaltation of clinical research is not some instinctive reaction by those who have spent long years acquiring knowledge of disease to relative upstarts such as biochemists who seem so often to be the modern wizards with some of the best contemporary scientific tricks. But even if this vague surmise were true, it would not be necessary to take it too seriously for those who work with patients have great opportunities for increasing knowledge, although clearly there are limitations on

doing fully planned experiments. There are numerous examples of how observations on patients have started off some of the most fruitful experimental researches—that on vitamins, which I have already mentioned, to give only one instance among many—but the true fruit was only obtained when experiments on animals combined with biochemistry could be done.

Sometimes the human being has been the only available subject not only for the discovery of a disease entity but for its subsequent investigation. Thus the great increase of recent years in knowledge of the anaemias has been acquired by observations on patients in the wards and from examinations of the blood conducted in the laboratory. Investigation on man of the upset of an intricate mechanism which is involved in pernicious anaemia had yielded most gratifying results. One may reflect, however, that the relative slowness with which they were obtained is a result of the fact that no animal is available showing the same defect as man, so that experiments must necessarily be of a limited nature. It is all the greater triumph of experimental ingenuity to be able to assay intrinsic factor on human beings, as can now be done relatively conveniently and safely by means of radio-active cobalamine.

The trial of drugs on man has now become systematised, for with the help of statisticians it is possible to plan assessments of the efficacy of drugs and even other methods of treatment which are far better than what are called "clinical impressions." These controlled clinical trials are a product of the twentieth century and are of the greatest use in contemporary practical medicine, but their intellectual value should not be over-estimated, for discoveries have to be made before any trials can be instituted and the trials can merely assess drugs discovered already or other systems of treatment already proposed. Controlled clinical trials can decide whether or not a method of treatment is efficacious or whether one method of treatment is better than another. They cannot discover new methods of treatment.

STATISTICS

Clinical trials depend primarily for their success on the fact that they are statistically controlled. A striking phenomenon of twentieth century medical science is the incursion of statistics into much quantitative biological work for the very good reason that there are few absolutely fixed quantities in many biological systems so that mathematical devices are needed to manipulate data before they will reveal the truth behind them. No one can deny the great impact that statistical thinking has had on medical research, but I am somewhat sceptical that great discoveries are going to be made by collecting information about the behaviour of man and his diseases and then

subjecting it to statistical analysis. All must be familiar with the difficulties in dealing with data obtained from man, and one can sympathise with those who collect and assess them. The difficulties are well illustrated by the doubts which have arisen on the interpretation of the statistics which purport to demonstrate the effect of smoking cigarettes in causing cancer of the lung. Another example is the considerable uncertainty that surrounds the attempt by statistical analysis to relate diet to the prevalence of atheroma and coronary thrombosis.

In spite of what I have said I know, of course, that good observation even with simple means, provided there is an acute intelligence, may still make real discoveries without the participation of the laboratory. There is no better example of this than the recognition that German measles contracted by the mother in the early months of pregnancy can result in foetal damage, a discovery made by an ophthalmologist who saw the connection between congenital cataract and infection of the mother. The recognition of retrolental fibroplasia in premature infants as being caused by excessive oxygen tension in the atmosphere surrounding the babies is another first-class example.

INFLUENCE OF WAR

One cannot consider twentieth century medical science without mentioning the two devastating wars waged on a gigantic scale which have marred our times, so that now political equilibrium seems difficult to attain. Surgery, anaesthesia, and preventive medicine, however, benefited greatly from these wars. The needs of war stimulated the investigation of blood transfusion, and again it is to laboratory work that we largely owe the present relatively happy position. The discovery of blood groups at the beginning of the century and their continued elucidation since then laid a firm foundation for the safe clinical use of transfusion, which was practised on an unprecedented scale during the last war and was in large measure responsible for the greatly improved prospects of survival of the wounded. There can be no question that the medical advances stimulated by war resulted in a saving of lives that far outweighed the destruction of life in war. Whether this could happen again in a third twentieth century war is for obvious reasons doubtful.

EFFECT ON POPULATION

Eastern countries demonstrate one of the great triumphs of twentieth century medicine, based on work which was initiated at the end of the nineteenth century. I refer to the diminution in the amount of malaria already

brought about and to the possibility that the disease may now be completely eliminated. The elimination of the mosquito which was recognized by laboratory work to be the carrier of the parasite of malaria was made possible by the elucidation of the habits of the species of mosquito involved, and the discovery of chemicals not too toxic to man and animals which were capable of destroying the insects. In addition, synthetic compounds have been produced which have, to all intents and purposes, displaced quinine as a chemotherapeutic agent. Chemotherapy of some other tropical diseases has also been strikingly successful.

One should not suppose that the remarkable advances made in the prevention and the treatment of disease caused by micro-organisms of all types in this century have been an unmixed blessing to the human race. They have, in fact, brought great social and political problems in their train. There is now occurring a spectacular increase in the population of the tropical countries and to a lesser extent in those of the temperate zones. It is true that optimistic people calculate that if we used the full resources of the world, enough food could be produced to keep up with the startling increase in the human population, but little attention is given to the enormous capital outlay which would be necessary just to keep up with population increases, let alone to make inroads on the malnutrition which is so widespread in some countries. Medicine, in a sense, has been too successful, for it has thrown out of adjustment a crude biological check on the increase of population; whereas pestilences and hunger used to keep populations down, the risk of infection has now been substantially reduced and nothing effective has yet been devised to take its place. There is evidence that serious attention is now being paid by politicians to the question of over-population, but I need hardly say that the control of population is not only a scientific matter, but that since it touches on the religious beliefs of some of the communities involved, it has very wide implications and difficulties. Nevertheless, twentieth century medical science recognized and talked about the problem and is now expanding researches aimed at bringing population into relationship with resources.

SCIENTIFIC LITERATURE

It may be worth examining another difficulty to which the vast scale of research and the consequent many additions to knowledge are leading. The literature of medical research alone is now so vast that it is quite beyond anyone's capacity even to glance at all of it. Many people adopt the very simple device of not reading anything except what is written by their friends or by people whom they think they may by chance meet some day.

That is certainly a simplification, but I think in all seriousness that we are reaching the point at which all except the most outstanding discoveries will be repeated at say 30-year intervals. We have reached the stage when our physicist colleagues are endeavouring to produce electronic machines which will be an extension of our brains, and when one reads that such machines can already translate Russian into crude English, which is more than most of us can do, and that there is a machine which has a fair knowledge of French grammar, one may hope that some of the difficulties of collating experimental data and drawing conclusions from them may be lessened by the methods of cybernetics.

But I must not look into my crystal ball because I note that this afternoon speakers are going to look into their crystal balls and to tell us what the future of medicine is to be.

EUROPEAN TRADITION

The twentieth century medical science that we are considering is based on the tradition and the discoveries of nineteenth century Western Europe. From there, modes of thought were transplanted to the United States, which has made so much of this inheritance that workers in this country are, there is little doubt, now surrounded by the most stimulating scientific atmosphere in the world, and their production of new knowledge in all the sciences that have a bearing on medicine is prodigious. This great growth of medical research in the U.S.A. is one of the outstanding features of twentieth century medicine. It may not be uninteresting to enquire why this development should have occurred. There is of course the innate vitality of the United States, but what strikes one in coming here from another country is that a substantial number of the populace has grasped the idea that research can lead to the solution of even the most recondite problems. Not only is there this general awareness of the possibilities of research, but those who control sources of money are eagerly helping medical research, and not least important of these are a substantial number of your legislators. It is perfectly true that money will not necessarily buy results, but it is quite certain that if insufficient money is put into research, results are much more difficult to obtain, for there is a great waste of energy in finding the wherewithal to carry out research and in making do with less than the best. Perhaps most important, rare original talent becomes much harder to foster than it should be. I am afraid that in many countries, including Great Britain, the money available for medical research still falls far short of what could be utilized.

It is to be noted that practically all the advances of twentieth century medicine have come from Europe and North America. This can only be because the experimental method has been vigorously exploited in these countries and because sufficient encouragement and freedom for thought have existed for investigations to be pursued with relative facility. Although it is a fact that the millions of the Far East have contributed little to modern medicine, one should not suppose that scientific capacity is confined to the western world, for it is demonstrably true that it is not, as a recent study of the history of scientific thought in China has reminded us. At the present time Eastern countries are taking up Western experimental methods with growing enthusiasm, and although they have as yet produced few new discoveries, their universities and government research institutes are firmly committed to the experimental method. There is little doubt that, as facilities expand, results will emerge from countries which now contribute little that is new to medical thought.

MEDICAL EDUCATION

What of the teaching of the rapidly expanding corpus of knowledge to medical students? I am not offering any solutions or suggestions, but perhaps we should keep in mind that the prime business of most medical students is eventually to look after the sick and to plan to keep communities healthy. They will not themselves be making discoveries, yet if they do not know how they are made, do not know how research is done and what may reasonably be expected in given situations, they will be hopelessly at sea in assessing the continual additions to knowledge which will confront them for all their lives, and they may easily become the victims of propaganda. We can talk airily about educating students and not instructing them, but unfortunately one cannot be educated without first being instructed at least in how to read and write. It is the combination of education and instruction that is so important.

Perhaps you in this country with your admirable postgraduate arrangements have come nearest to a really modern solution of this problem, for you have succeeded in producing a medical elite which not only understands that it is the patient who needs consideration but is equipped with sufficient basic training to be able to conduct experimental research in the laboratory to illuminate phenomena noted in patients, and you have come nearest to making your practitioners who treat patients have a real scientific outlook.

You may have noticed that I have mentioned only one name, and that was Ross Harrison who worked at Yale. I have done this deliberately to emphasize that the basis of twentieth century medicine has been furnished not only

by a few outstanding figures but by the work of thousands upon thousands of people who have contributed, or are still contributing, in greater or lesser degree to the present accelerating search for knowledge.

Present-day medical science can perhaps be likened to a gigantic vat containing liquid in which fermentation is actively proceeding; small and large bubbles of gas rise to the surface only to burst and to be of no consequence, but all the while the liquid is being enriched by products which on subsequent distillation yield a small quantity of spirit of rare quality. So from the great volume of contemporary investigation some well-established facts emerge which form the basis for further advances. In medical science such advances will come in the main from the further progress of physics, chemistry, and biology.

To sum up I suggest that the historical lesson of twentieth century medical science is that the application of experiment will unlock many doors, that experiment is the most efficient method for acquiring new knowledge that we know of, and that all our efforts should be devoted to expanding its scope in the laboratory and in the clinic.

Articles are accepted for publication in *The Yale Journal of Biology and Medicine* on the basis of merit and suitability. The privilege of submitting articles is not limited to those associated with Yale University and contributions from others are cordially invited.

The Board of Editors

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MEDICAL SCIENCE AND THE FUTURE†

In 1810 when this School was established the average expectation of life of a child born in that year was 34 years. A child born today can look forward to a life span of somewhat more than 70 years. Thus the expectation of life of Americans has doubled during the 150 years of the existence of this School of Medicine.

Only 50 years ago the death rate from all causes was twice as great as it is today. In the case of certain diseases medical research during the last half century has brought about almost unbelievable reductions in the fatality rate. Pneumonia, termed by Osler at the beginning of this century as the most fatal of all infectious diseases, now has a mortality rate about one tenth of that prevailing at that time. Deaths of children from infectious diseases are only a fiftieth of that at the beginning of this century while death from the hazards of childbirth has fallen to a comparable extent.

When I became a medical student, and I hasten to add that this was less than 50 years ago, I was taught that severe diabetes and pernicious anemia were incurable diseases. Surgical intervention for brain tumors was regarded as a hazardous procedure to be attempted only by very few. The surgical relief of certain types of heart disease, whether congenital or acquired, was not even contemplated. Today we all know that diabetes and pernicious anemia are controllable, while the extraordinary achievements of surgery, not only in the relief of diseases of the central nervous or circulatory systems but in other previously unapproachable areas of the body, excites our awe and admiration.

It would seem quite appropriate, therefore, that when we are gathered to celebrate the 150th anniversary of one of the schools of medicine in this country, we should inquire into the reasons why these remarkable changes in our ability to subdue at least some previously fearsome diseases has come about. We do this recognizing that much remains to be accomplished. Cancer, heart disease, and the distressing consequences of mental disease still exact a large and increasing toll. Nevertheless, the achievements of

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the last fifty years give us hope and confidence that they too can be subdued by the continued application of the same methods that have proved their worth in the alleviation of other, formerly serious, diseases.

THE PRESENT SCOPE OF MEDICAL RESEARCH

While there are many factors that have contributed to the improvement in the public health, such as adequate diet, better housing, and sanitation, few would disagree that the major contribution to our capacity to prevent and treat disease has come from advances in medical science.

Fifty years ago, research in the medical sciences was confined largely to the departments traditionally associated with the medical schools themselves. Nowadays every one of the biological and physical sciences, in some way or another, is contributing or has contributed, information of the greatest importance so far as our understanding of disease processes is concerned. The reason for this is that it is now appreciated that living cells from the lowest to the highest forms of life carry out their manifold activities by virtue of the chemical and physical reactions that take place within them. Even more remarkable is the finding that many of these basic chemical and physical phenomena are common to all types of cells, differing only in detail rather than in the general principles of their operation. This means that information gathered from the study of bacteria is of value in an understanding of the function of cells of all species, including man himself. For example, our knowledge of the chemical nature of the genes and their mechanism of action in determining the replication of cell types has been gained very largely from a study of microorganisms.

Also it is unnecessary to remind this audience that our most efficacious agents in the control of many infectious diseases, the antibiotics, are metabolic products produced by the simpler forms of living organisms. This concept has given us confidence that the study of all forms of living things from the lowest to the highest does have and will continue to have a pertinent relation to our understanding of the normal and abnormal functions of man himself.

Many years ago Aristotle said "And so it happens, as I think, that most natural philosophers and those who have a more philosophical understanding of their science, end in the one case by investigating medicine and in the other begin with deductions from the laws of nature and their application to medicine."

This I think expresses the present day scope of medical science as well as it can be stated. Those directly concerned with the problems of the control of human disease are turning to the basic sciences for assistance, while

the basic scientists themselves are finding that the knowledge they uncover concerning the vital processes of lower organisms are becoming of the greatest value in the understanding, prevention, and treatment of disease in man.

THE SUPPORT OF MEDICAL RESEARCH

The fact that knowledge useful in the cure and prevention of disease is to be obtained by research in all fields of biology, in many fields of physical science, as well as in the behavioral sciences, is now accepted not only by scientists but by all agencies, public and private, that are entrusted with funds to be dispersed to promote the health of the nation. The implications of this for the future are far reaching. In the first place the people of this and other countries have become aware that it is not inevitable that they should continue to suffer death and disability from disease. They have learned that there are available, in increasing number, measures which in many instances can either alleviate or cure some of the major diseases that have plagued them for centuries. To secure this end the people of this country have and are contributing, through government or private agencies, money in amounts unparalleled in history and it is safe to say that in the future this support will not only continue but will be on an increasing scale. We as a people have learned, perhaps somewhat belatedly, that expenditures for our defense against the internal enemies of disease are as vital to our existence as those for our defense against the external foes who threaten us.

The confidence of the public in the gains in health and prolongation of life to be expected from intensified and continued investigation into the nature of disease is reflected in the extent of their financial support of such endeavors. This year nearly 750 million dollars of private and public funds will be available for these purposes and of this sum government agencies will contribute at least half. During the last fifteen years private agencies, collecting money directly from the public and devoting these funds to the investigation of disease, have not only increased in number but in the total amounts of money contributed. In other words, the large increase in contributions from the Federal government for the support of medical research has not, as many feared, decreased private philanthropy but has actually increased the monies from this source.

The great increase in the funds available for medical research has enabled a variety of types of support of medical research to be undertaken. In addition to direct grants for the conduct of investigations, they include provision of fellowships, long term support of established investigators,

funds for training in various fields, and participation in the construction of research facilities.

These funds have not, as often supposed, gone entirely to medical schools. At present more than half of the money made available through the National Institutes of Health is given for work in university or college departments not identified with medical education. Nonetheless, the major part of these funds are going at the present time to our educational institutions and the question has already been raised as to how much more research they can absorb without damage to their other responsibilities. Without, at the moment, hazarding an opinion on how much more research supported by restricted funds any institution can or should undertake, let me say that up to the present these funds have had, at least in my opinion, a stimulating effect on those departments of our educational institutions where they have been available. They have without doubt made possible the training of many young scientists who otherwise might have been lost to us. They have provided the facilities and expensive equipment upon which so much of modern research depends and they have been responsible for a greatly increased completion of research programs, if this is judged by the number of papers appearing in scientific journals.

It has been said that the funds available for research, particularly in the diseases most feared, such as cancer and heart disease, are in excess of the needs of the number of qualified investigators in these fields and that in consequence much of the work produced is of a marginal or trivial character. This seems to me to be an inadequate basis for restricting public or private support of these endeavors. In the first place we are expending vastly greater sums on other enterprises which, while they may be necessitated by the conditions under which we now live, promise far less for the future betterment of mankind than does the support of medical science. Also, as I have already stated, a large proportion of the funds collected or appropriated for special disease research are used to support basic research, for example, in such fields as the investigation of processes controlling growth in normal tissues and organisms. Unless we learn more of the complex mechanisms underlying cell growth and division our efforts to solve the cancer problem will be dependent on the vagaries of empiricism or on luck, neither of which commend themselves as an intelligent approach to a problem of this magnitude. Furthermore, is it not better to be overspending than underspending when the stakes in human welfare are so high. Even if success against the major diseases be delayed, as it well may be, is it not still the path of wisdom to use money to expand human knowledge by increasing both the numbers and opportunities for gifted individ-

uals engaged in the study of natural phenomena. The record of the past reveals that every gain in knowledge in any field of science will in time touch and illuminate the unknown areas of others. Some of this knowledge will be immediately useful and may, as we all hope, increase our ability to control disease. Some will have no immediate practical value and will remain in the archives of science for many years until one day they may provide the key to discoveries of immense importance to future generations.

PRESENT AND FUTURE PROBLEMS

While we strive to increase our understanding of the nature of living things and by so doing increase our knowledge of the causes and means of prevention of disease we should also be aware of some of the consequences of success.

The reduction in the incidence and severity of many diseases that has followed the extraordinary accomplishments of medical research in the last fifty years has raised in its wake problems of another kind. Chief among these are those resulting from the explosive growth of population in underdeveloped countries whose food resources were already strained to their capacity. Even in this country we have seen a startling increase in the number of those who used to be regarded as the elderly group of our citizens. Since heart disease, cancer and the so-called degenerative diseases occur to greater extent in the later decades of life, we now have an increasing concern and pressure to find the means to control them. Discovery of these would increase still more the proportion of our people who live beyond the biblical years of life.

The social and economic consequences of a reduced mortality rate and a consequent extension of the life span are forces that cannot be ignored. Suppose we were able to control or materially reduce the mortality from disease to the point where the average expectation of life was increased to 90 or even 100 years. This is not an impossibility and indeed is implicit in our hopes for the conquest of those diseases that at the present time are the major cause of death. Since it may be presumed that such an extended life would also be associated with continued good health, such an eventuality would have widespread repercussions on the structure of our society.

However, I am not proposing that for this or any other reason should we limit the extent or support of medical research, any more than the construction of nuclear weapons should be a reason to cease physical research. Rather I am suggesting that the continued progress of scientific knowledge derived from research is the factor that will determine the future pattern of our society. We should be prepared to accept not only the benefits but

the changes that this new knowledge will bring. Furthermore, this generation must order its affairs as to ensure that future generations will possess both the scientists and the facilities to carry forward what has been so well begun.

The provision of adequate facilities for now and the future is the easiest part of our responsibility. We need, even at the present time, more and better equipped laboratories than we possess. We are in need of a large scale rehabilitation of our facilities for the training of students and the conduct of research. To provide these is essentially a question of money but to ensure an adequate number of well trained imaginative and dedicated scientists devoted to basic research is a task of somewhat greater complexity and one that provision of adequate funds, while essential, will not of itself meet our present and future needs.

This country needs large and increasing numbers of people trained in science to operate its technology and professional services. The provision of an adequate number of physicians, which is becoming a compelling problem, is but one example of our need for highly trained and skilled individuals whose professional competence is to an increasing degree dependent on an adequate scientific background.

To provide expanded and adequate facilities is the easiest part of our present and future responsibility. To cultivate a general understanding of the purposes of science, to select and train an adequate number of imaginative and dedicated people for a career in basic research is a task of greater complexity. True we need adequate funds for this just as we do for facilities, but the mere provision of money in itself is not the complete answer although I would be the last to deny that without it there would be little chance of improvement.

Our hopes for the future progress of medical science can be fulfilled only to the extent to which we are prepared to support our educational institutions. We depend on these not only to carry out the largest portion of basic research but to train the increasing number of basic and applied scientists that will be needed.

On an occasion such as this it is always a temptation to make optimistic forecasts as to how soon we will achieve the conquest of those diseases that are such a present concern to the public. I will refrain from such speculations except to say that I doubt if all the major problems of disease will be solved by this generation. Consequently, while we should continue to develop and expand medical research, we should not do so in a way that will impede or divert our educational institutions from their primary purposes. These purposes are first to provide for the education and training of young

men and women so that in due course they may make their own contributions to knowledge; secondly to provide an environment in which scholars may not only choose their field of endeavor but may pursue it without thought of practical results. Hasty and ill advised pressures prompted by emotional urges to do something to relieve our fears of disease may, in the long run, be disastrous to the orderly progress of science and inflict irreparable damage upon our educational institutions.

Over and above these needs, however, is the necessity to identify, train and support the much smaller group of men and women who by virtue of their special gifts of insight, imagination and dedication to their work qualify as research scientists. By this term I mean those individuals who have the capacity to carry out exhaustive and critical investigations which do result in new knowledge and the formulation of new laws of nature.

The reasons that attract one individual into a lifetime spent in basic research while another of apparent equal ability finds no interest or happiness in such pursuits are almost impossible to formulate. In my own experience I would place the inspiration for the choice of such a career as being most frequently engendered by an association in the formative years with a teacher having great capacity not only to present scientific material but to do so with an enthusiasm that kindles in their pupils a desire to join in what is presented to them as an exciting and rewarding venture into the unknown.

There are of course other reasons. Some individuals come into research by accident, some in later years when they realize that the problems of their professional life are insoluble without further knowledge. Whatever may be the reason for choosing a career in basic research the number who do so will be relatively small. Nonetheless our hopes for the future of medical science as for advancement in all sciences depends upon them. Consequently, we should be giving our best thoughts and efforts not only to find such individuals but to assure that neither financial stringency nor any other reason prevents them from obtaining the training, facilities, and support both spiritual and material to sustain the hard work and lonely life that those who pioneer in the expansion of knowledge often encounter.

If this can be done and our educational institutions can receive the additional support to provide such opportunities then I am convinced that the present grave problems presented by cancer, diseases of the circulatory system and by mental illness will in time be resolved. This is not to say that other problems of human illness will not arise or that the present ones will entirely disappear. After all we live in a hostile world and while it is unlikely that we will ever be secure from the inroads of our environment

we may, at least in time, learn to control and mitigate their effects. As one of my particular scientific heroes the late Professor E. H. Starling once wrote "Only labor is required to extend almost without limit of our understanding of the human body and our control of its fate."

The recognition that the pursuit of science is a proper field of human endeavor regardless of its utilitarianism is the mark of an enlightened people. While it is true that scientific research will advance human welfare this is not the only justification for its support and encouragement. As Sir Richard Gregory has said "science is not to be regarded merely as a store house of facts to be used for material purposes, but as one of the great human endeavors to be ranked with the arts and religion as the guide and expression of man's fearless search for truth.

It is in this light that we must appreciate the role of medical science in our future. In the light of what has already been achieved we can, with confidence, assume that in time it will afford the means for further relief from disease. Working in association with all other branches of science it can give us an almost unlimited insight into the nature of living processes; an understanding of the way in which living creatures evolved from complicated molecules to man. It can point the way to a world in which man, freed from ignorance, superstition and fear of disease, can begin to utilize his knowledge for the betterment and happiness of all races.

As we go forward towards the bicentennial of this School let us do so with a profound appreciation of our predecessors whose labors raised this School to its present level of excellence. Our foundations are strong because we are part of the great University that founded, nourished and had faith in our goals even during our most difficult years. Let us hope that those who will meet to celebrate future anniversaries will be able to say that we, the present generation, did not fail them; that our efforts as teachers and investigators contributed to what I am sure will be a body of scientific knowledge concerning the function of living things, and a capacity to treat and prevent disease that is beyond our wildest dreams.

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CLINICAL MEDICINE AND THE FUTURE†

The only certainty about the future of clinical medicine is that it will constantly be undergoing change. On the one hand it responds to the ever-expanding body of clinical knowledge, and on the other to the varying political and economic situations of the world. I shall be concentrating today on our increasing understanding of medical phenomena; nevertheless, simply to illustrate the influence of economic factors let me remind you of the kinds of medical problems that present themselves in different parts of the world today. There are places where the average span of life is short, and where the principal health problems are caused by inadequate food or infectious diseases such as typhoid fever. By contrast, in a large Western city some of the major medical problems are provided by automobile accidents, air pollution, obesity, alcoholism, hypertension, and the disorders of old age. Clearly then, clinical medicine is bound to be influenced by the changing economic, technical, political and social developments of this turbulent world; most of these are quite beyond the influence of members of the medical profession.

Now to take up the aspect of the future that we *can* influence. Let me first describe the methods by which our existing body of clinical knowledge has been obtained. I believe it fair to say that there was little understanding of the mechanisms of disease prior to the beginning of the last century. Then, stimulated by the example of clinicians like Richard Bright, men began to correlate the manifestations of illness with pathologic changes in different organs. This simple method of observation has been responsible for the accumulation of a large mass of factual information about disease.

The next step was the application of laboratory methods. First came the new science of bacteriology, almost immediately adapted to clinical medicine; then physicians began to realize that additional help could be gained from the techniques and knowledge of chemists and physiologists. At the end of the century the discovery of X-ray found clinicians everywhere ready to

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take immediate advantage of a new means of elucidating the phenomena of illness.

Along with growing understanding of pathologic processes came some improvements in therapy, usually it must be confessed, as a result of chance observation. The most notable of these of course was surgical anesthesia, which permitted operations to be performed deliberately and to be undertaken on an elective basis. This was the major factor enabling surgery to develop into the wonderfully skillful thing it is today.

So by the end of the last century our main methods for study of clinical medicine had been worked out. We of the twentieth century can point only to certain modifications and improvements. For example we have fostered the development of a new kind of scientist: the clinical investigator. Previously all studies of clinical medicine had been carried out merely when convenient, and incidental to the demands of private practice. Now, paid by salaries and usually specially trained in basic medical sciences, clinical investigators are in a favorable position to learn about disease.

Another contribution of the present century is a great expansion in the total effort of medical research. This came about as a result of changing political and economic circumstances. During the Second World War came the demonstration that by massive expenditure of funds and manpower certain specified scientific goals could be achieved; examples are the atomic bomb, radar, and the manufacture of penicillin. From this experience the inference was drawn that disease problems likewise could be solved by spending large sums of money on medical research. Federal agencies and private foundations, especially in our own country, began in the late 1940's to provide support on a scale previously unknown. Industry, too, began to invest in medical research, on finding that the development and sale of drugs such as antibiotics, steroid compounds, and tranquilizers could be very profitable.

Thus we have seen within the past few years an unprecedented infusion of manpower and funds into clinical investigation, and into related scientific fields. The result has been a series of changes in clinical practice so remarkable as to be difficult to appreciate, even by those of us who have been active participants. To emphasize this I propose to spend a few minutes in a review of some of the high points within my own professional experience.

Let us imagine a Dr. Rip Van Winkle, who has just awakened after a twenty-year sleep, and sets out to visit a teaching hospital. He would find many more doctors working there, and would observe also that the buildings have been enlarged, not to accommodate more patients, but to house laboratories and special treatment facilities. He would be unfamiliar with

the institution known as the Blood Bank, and would be amazed to learn that the hospital now has devices which can substitute temporarily for the human kidney or heart or lung.

In the operating rooms he would observe impressive developments in anesthesia, and would learn that hypothermia or hypotension are now sometimes deliberately induced during major operative procedures. Some of the surgery he would hardly have thought possible: for example, reconstructive procedures within the chambers of the heart. He would be surprised to find that long confinement in bed after major surgery has been abandoned, and that patients now often stand or take a few steps on the first postoperative day.

In the medical wards of the hospital the visitor would find that the average age of patients is about 20 years greater than in 1940, due principally to new treatments for infectious disease. He would be delighted to find that certain serious infections like bacterial meningitis or endocarditis, which he had regarded as usually fatal, are now looked upon as curable.

One of the most impressive changes would be virtually new pharmacopoeia. Of the drugs which were in common use in 1940 the principal survivors today are morphine, the barbiturates and aspirin. Even digitalis appears in new purified forms. The antibiotics and steroid compounds, both unknown to clinicians in 1940, now account for the majority of all prescriptions. Other impressive innovations include diuretics, so effective that the clinical picture of dropsy has become comparatively rare, and drugs which can, temporarily at least, retard the progress of some kinds of cancer.

In the realm of diagnostic procedures the visitor would doubtless be appalled by the increased number and complexity of tests. Whereas in 1940 a basal metabolic rate determination seemed about the ultimate in physiological measurement, cardiac catheterization has now become commonplace. In the X-ray department he would find pieces of equipment being used for unfamiliar examinations such as cinefluorography. In the chemistry laboratories it would be apparent that clinicians now consider essential many determinations he never used, such as measurement of blood sodium and potassium. The chemical equipment itself would be mystifying, with its electronic systems of measurements, and techniques like electrophoresis.

So much for Dr. Rip Van Winkle. I felt it worth while to devote some of this discussion to the past because I believe that only by considering the circumstances that have brought us to our present position can we hope to make reasonable guesses about the future. I emphasized the great changes

we have witnessed recently to show the ferment of activity that is in clinical medicine today. We can expect this state to continue—indeed probably even to be magnified—so that medical practice in the forseeable future is likely to change almost beyond recognition every generation or so.

Now what is our long-range goal in medical research? It is to obtain knowledge that will enable us to define accurately the various factors and events that lead to the development of different kinds of disease. With that kind of information we can hope to devise effective means of prevention or treatment.

Short of the goal of complete understanding and rational treatment, we may, of course, be able to alleviate the manifestations of disease, as for example, when we use a steroid compound to suppress an intense allergic reaction. In this phase of practice we can anticipate a series of discoveries which will have practical value. One of the major obligations of clinical investigators is going to be the careful appraisal of new compounds, so that their full range of effects on human beings can be determined as quickly and safely as possible. The pharmaceutical industry will direct to us a steady flow of new antimicrobial preparations, steroid hormones and drugs affecting mood, consciousness or pain sensation, as well as drugs to raise or lower blood pressure, or to influence the excretion of salt and water.

What lies ahead for surgery? At present it seems that most surgical procedures can be placed in either of two categories: repair of injury, or removal of diseased tissue. Repair of injury is presently being exploited with considerable success in the field of cardiovascular disease. We can anticipate great technical advances in open heart surgery, and in replacement of diseased arteries by plastic tubes. We can hope that better procedures will be devised for improving the circulation of the heart itself.

In respect to surgery for removal of diseased tissue, it seems to me we cannot look forward to greatly improved results. Of course there will be technical advances, and, without doubt, this kind of treatment will be the best available for a long time to come. Nothing now in sight promises to substitute for removal of an inflamed appendix, or an enlarged prostate, or a cancerous bowel. But our hope should be to make that kind of treatment obsolete. It has already been accomplished to some extent in mastoiditis and hyperthyroidism.

There is in sight the prospect of a great *new* field for surgery. Instead of plucking out the diseased part the surgeon will substitute for it a healthy tissue. This has actually been achieved already, under special circum-

stances, in that a normal human kidney has been transplanted successfully into the body of a person with severe renal disease. The obstacle to be overcome before this can be employed on a wide scale is the curious allergy exhibited by each of us to acceptance of a graft from any other person. This immunological reaction usually results in rejection of the transplanted tissue within a few days. The phenomenon is under intensive study by immunologists all over the world. Only last week the Nobel Prize in Medicine was awarded to two scientists who are working in the field. I am confident that a solution will be found, so that the transplanting of tissues and organs from healthy to diseased persons will be a practical method of treatment within the next decade or two. When that happens the possible applications are almost limitless.

Among medical diseases one might predict that substantial progress is to be made soon in some genetic diseases, the so-called inborn errors in metabolism. Real advances have been achieved within the past decade by workers in the fields of microbial genetics and nucleic acid chemistry. Clinicians have begun to develop better techniques for study of genetic disorders in man. There is every indication that some of these conditions are caused by simple and identifiable biochemical defects perhaps involving single enzyme systems. Detailed knowledge of these should lead to effective treatment, perhaps merely the administration of some substance the patient cannot make himself. This would be comparable with the cure of a deficiency disease by giving the appropriate vitamin.

Arteriosclerosis becomes relatively more and more important in human disease, because of the steadily lengthening span of life. Much work has been done on this problem, both in man and in animals. Of the possible causative factors, diet, endocrine function, blood pressure, race and environment have received special attention. Their relative importance is being disputed at present; nevertheless some progress is being made. That diet seems to play a role gives us reason to believe that preventive and even curative treatment are not beyond possibility. What we must have is better understanding of the events leading to deposit of fatty substances in arterial walls.

There is reason for hope also in connection with another important cardiovascular disease: hypertension. Here, too, we deal with a disorder of complex and variable etiology, but it is susceptible to study in animals and in man. Information about its humoral and neural mechanisms is growing. Even now we have drugs of some value in management of the most serious forms of hypertension. The eventual prospect for control of the disorder is good.

What about the outlook in the cancer problem? Here we have a diverse group of diseases, where multiple factors seem to be involved: heredity, endocrine function, chronic irritation, virus infection, and possibly immune mechanisms. The role of these, and doubtless other factors, needs to be defined far more clearly than at present. Experiments in animals are of value, but the findings are difficult to interpret in terms of human disease. Our present methods of treatment, surgery and radiation, while curative in some situations are worthless in others; and I see little prospect that these methods can be made a great deal more effective. We all hope that some kind of chemical approach to treatment will eventually be developed, and indeed this is an active field of investigation. Much of the work, however, is nothing more than blind trial-and-error; at best it is based on what might be called educated guesses. Here and there encouraging results have been obtained, but I fear we must expect neoplastic disease to be an important cause of death for a long time to come.

I turn now to the problem of mental disorders. Neuroses and psychoses certainly account for a large share of all suffering and disability. Considering their great importance one may wonder why so little research is being done in the field. An obvious explanation is the problem of finding something with which to work. Animal experiments have severe limitations, there is no recognizable pathology to correlate with symptoms, and laboratory tests have thus far yielded nothing significant. Faced with this situation the psychiatrist must do what he can on the basis of clinical observation alone. When we stop to consider that mental disorders are likely to be the product of such intangibles as heredity and the individual's total life experience, we can appreciate the vast difficulties that must be met in comprehending psychiatric illness. Quite understandably the field at present is characterized by disagreement. To be sure, in the matter of treatment some progress has been made, but the methods are so cumbersome and expensive that they scarcely affect the total problem of psychiatric illness. Some of the recently introduced drugs which affect mood and behavior have eased difficulties in patient management, and we can expect further progress in that direction. But in terms of the goal of understanding-in-depth psychiatry seems to represent a far more difficult problem than we have in many other branches of clinical medicine.

The last subject I shall mention specifically is that of aging. Here I believe we must be willing to expect defeat. There is little reason to hope we shall ever see exceptions to the general law that all living things eventually deteriorate and die. Neuropathologists tell us there is a net decrease

in number of nerve cells in the brain every day of our lives after the third decade. Other parts of the body must also suffer steady impairment, simply from the ordinary buffetings of living. Although I have just been predicting the discovery of methods to combat coronary artery disease and hypertension there remains the probability that one day, the heart, after beating 70 times a minute during a long life, will just wear out.

So much for guessing about the future. I have been seeking to picture a sort of spectrum among the major disease problems. At one end are those where causative mechanisms can be identified, where good tools for study are available, and the prospects for control seem relatively good. At the other end are those which develop insidiously, probably because of multiple inter-acting forces. These are generally difficult to study, and progress seems likely to be slow in coming.

The 150-year span of time that we celebrate today has seen important changes in the picture of human disease. A crude understanding of causative mechanisms has been gained, and some effective forms of medical and surgical treatment have been developed. In a few areas, notably the infectious diseases, endocrine disorders and nutritional deficiency diseases, we are able to speak in terms of curative treatment.

Just how far *have* we come in 150 years? In particular, how will those who follow us look back upon the present period? Despite its activity, I think this will not be regarded as a Golden Era in medical science. Its most notable aspect is simply the stepped-up tempo of scientific investigation. We must not exaggerate the extent of our achievements merely because they have created such changes in the appearance of clinical medicine. Although we're glad we can relieve headache by prescribing aspirin we should not be satisfied until we know why it is that people with many different kinds of disturbance feel pain in the head. Unfortunately, most of our treatment is still in the aspirin-for-headache category. I pointed out earlier that dropsy is uncommon now because the diuretic agents we use are so effective, yet this is purely symptomatic treatment which has no effect on the basic disease of heart or liver that caused the retention of water. Consider how ignorant we are even where we have chanced upon a curative treatment, as with penicillin in pneumonia. We have little understanding of the ways in which bacterial infection of the lung produces its manifestations, and we have failed so far even to answer the simple question how penicillin interferes with bacterial growth.

We are therefore only in the early phases of a long search. With better understanding, prevention and cure of many important diseases will be

possible. Yet we must accept too that complete success can never be achieved. Better treatment for some diseases will increase the relative seriousness of the unsolved problems. Changing conditions in the universe will unquestionably bring out new medical challenges. I suppose we might look upon successive medical generations as riders in a never-ending Pony Express, none of them being privileged to reach the destination. This, however, does not seem to me a discouraging prospect. We can be confident that we are travelling in the right direction, with an overall result of steady improvement in the alleviation of suffering. It is satisfaction enough for any of us to participate in this combined effort, and to share the pleasure when anyone, anywhere, provides us with a little more understanding.

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Mitosis of Chondrocytes Induced in the Knee Joint Articular Cartilage of Adult Rabbits.*

By E. S. Crelin and W. O. Southwick, Department of Anatomy and Section of Orthopedic Surgery, Yale University School of Medicine.

Since Leidy's experiment,[6] numerous investigations have been made of the changes occurring in mature articular cartilage experimentally traumatized by incision.[1] Although one of the frequently described changes was an increase in the number of chondrocytes occurring at or near the site of injury, only two investigators[5, 6] reported finding chondrocytes undergoing mitotic division. These results differ from those of Elliott's study[3] on normal, mature articular cartilage, for he concluded that although mitosis is the method of cell division in growing articular cartilage, after growth ceases, amitosis becomes the rare but sole normal method of chondrocyte division. Recently, changes similar to those of degenerative arthritis were induced by compression in the knee joint cartilage of the adult monkey, rabbit,[7] and rat,[4] however, no chondrocyte proliferation was described.

The present experiment was designed to investigate the occurrence of chondrocyte mitosis in mature articular cartilage traumatized by sustained pressure. Colchicine was employed to detect the occurrence of chondrocyte mitosis, as in previous studies of the interpubic joint cartilage of pregnant mice.[2]

The articular hyaline cartilage of the right knee of ten adult rabbits was subjected to pressure in the following manner. Two stainless steel pins were passed transversely through the distal metaphysis of the femur and two through the proximal metaphysis of the tibia in the coronal plane. The two sets of pins were interconnected on both the medial and lateral aspects of the knee by a bolt and nut mechanism which, when tightened, rendered the knee completely immobile in a position midway between full extension and full flexion. The clamp maintained the weight-bearing surfaces of the right femoral and tibial condyles in direct contact under sustained pressure for 16 days. Eight hours before each rabbit was sacrificed, each received by intraperitoneal injection, 5 mg. of colchicine to arrest at metaphase any mitosis occurring during that time. The localized areas of articular cartilage which had been in direct contact under pressure in the right knees and comparable areas of articular cartilage in the untreated left knees were excised and sectioned serially at 8μ.

The sectioned cartilage from both the femoral and the tibial condyles of the clamped knees of three rabbits was in the following initial stages of reaction to the pressure: the matrix at the free surface of the cartilage was increased in amount, the free surface of the cartilage was roughened, the

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lacunae underlying the roughened surface were enlarged, and instead of each containing the usual single flattened cell, each contained from two to seven enlarged chondrocytes (Fig. 1A and B). An average of three chondrocytes per tissue section was found in metaphase of mitotic division in the enlarged lacunae (Fig. 1C). The sectioned cartilage from both the femoral and tibial condyles of the clamped knees of the other seven rabbits showed a localized breakdown in the area which had been subjected to maximum pressure. Numerous enlarged lacunae containing from two to ten enlarged chondrocytes were found in the intact cartilage at the periphery of the destroyed cartilage. An average of about two chondrocytes per tissue section was found in metaphase of division in these enlarged lacunae. No dividing chondrocytes were found in the sectioned cartilage of the untreated left knees.

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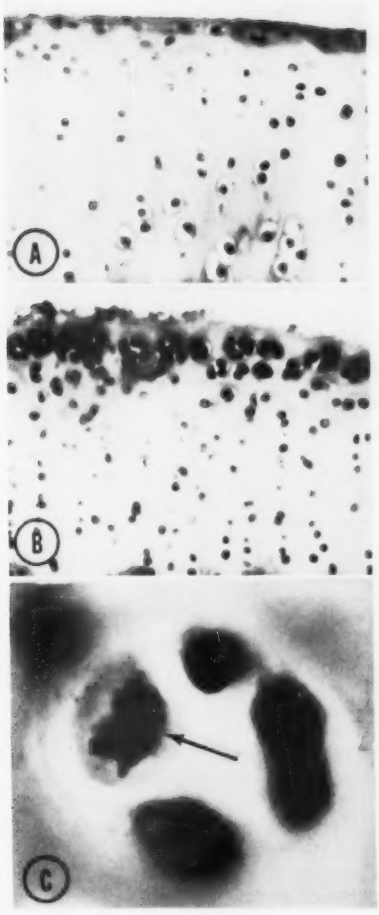


FIG. 1. Mitosis of chondrocytes induced in the knee joint articular cartilage of adult rabbits. A: Articular cartilage of the weight bearing surface on the medial femoral condyle of an untreated rabbit's knee (x432); B: Articular cartilage subjected to sustained pressure from approximately the same area of the femoral condyle shown in A (x432); C: Lacuna of articular cartilage subjected to sustained pressure containing five chondrocytes. One chondrocyte (arrow) is in metaphase of mitotic division (x1,000).

WOODWARD LECTURE

28 September 1960

AMINO ACID SEQUENCES IN PROTEINS. Dr. Frederick Sanger, Cambridge University. Nobel Laureate in chemistry.

Dr. Frederick Sanger presented a discussion of his current enzyme research involving the amino acid sequences surrounding the active centers. The enzymes studied in this work may be characterized by the fact that phosphate is incorporated into the protein structure in the normal enzymatic reaction as is the case for phosphoglucomutase, or else the treatment of the enzyme with diisopropylfluorophosphate results in a stoichiometric reaction incorporating phosphate into the molecular structure with consequent inactivation of the enzyme. Enzymes in this latter category include trypsin, chymotrypsin, elastase, and several others. Analysis of enzymes labeled with radioactive phosphate by the above methods shows that the phosphate has been coupled to the amino acid serine. This fact together with the observed inactivation of the chemically phosphorylated enzyme supports the assumption that the serine residue is present in the active center of the enzyme. The purpose of this work was to determine the amino acid sequence around this serine residue in phosphoglucomutase in order to compare it with the previously determined sequences in elastase, trypsin, and chymotrypsin.

The basic techniques used in these studies were the incorporation of radioactive phosphate into the serine residue as noted above, partial acid hydrolysis of the enzyme into component peptides, separation of the peptides by ionophoresis on filter paper, and the identification of the peptides around the active center by radioautography of the ionophoretic pattern. These techniques were supplemented by three maneuvers that allowed identification of the component amino acids in the peptides and the determination of the correct sequence.

By subjecting each of the radioactive peptides to acid hydrolysis and counting the number of radioactive products, the number of amino acids in each peptide was determined. Then, the position of the serine residue within each radioactive peptide was determined by using the Edman reaction which allows identification of the N-terminal amino acid of a peptide while leaving the rest of the sequence intact for further reaction. Finally, identification of the amino acids was accomplished in two ways. Either the pK value of the peptide was determined by plotting ionophoretic mobility as function of pH, or the Pardee formula was used which relates the R_f value of a peptide to the R_f value of the individual amino acid or peptide components.

Utilizing these methods, the sequence around the active center in phosphoglucomutase was found to be Thr-Asp-Ser-His-Asp. This sequence was confirmed by using methods similar to those employed in the study of insulin. Dr. Sanger emphasized the fact that the procedures illustrated in this study allow a more rapid determination of amino acid sequences without the time consuming purification of peptides necessary in the more usual procedures.

A. J. W.

PHYSICS AND MEDICINE OF THE ATMOSPHERE AND SPACE. Major General Otis O. Benson, Jr. and Dr. Hubertus Strughold, Eds., New York, John Wiley & Sons, Inc., 1960, 645 pp.

This book presents a number of papers read at the Second International Symposium on Physics and Medicine of the Atmosphere and Space, held at the School of Aviation Medicine in San Antonio, Texas in November 1958. The title of the book is misleading, as there are few papers that are related to "medicine." The characteristics of the "physics" papers vary widely. The review type of paper is well illustrated by L. R. Shepard's "Review of Possible Propulsion Systems," which gives the reader a concise outline of some of the principles and quantities involved. A number of papers deal with high-energy particles, while others are concerned with upper atmosphere composition and environment. The science-fiction type of paper shows up in "Time Dilation and the Astronaut," which merely presents a rehash of the apparent time paradox introduced by the equations of Special Relativity. Rather too many papers depend on "artist's conceptions" of possible space craft.

Among the biological papers emphasis is given to the problems likely to be encountered by future astronauts. Papers range from descriptions of experiments carried out on the "Effects of High Altitude Cosmic Radiation on Barley Seeds," by J. Eugster and D. G. Simons, to speculations on the use of algae in "Nutrition on Long Space Voyages," by R. G. Tischer. Other papers are concerned with the effects on the human body of large accelerating forces, and with the possible psychological problems which may arise in space flight.

As appears to be inevitable with reports from symposia, the better papers can provide little information in the space available. For the specialist such papers have little new to offer, while to the non-specialist they often are too condensed for ready application. The book jacket states that this volume promises to be "a major source of data" to workers in the field. It is to be hoped that this is not the case. However, to the generally interested scientific reader the book does offer a glimpse of some of the physical and biological problems associated with space flight. However, such readers would benefit from a more careful selection of the papers to be included in a volume of this type.

S. J. F.

SPACE BIOLOGY, THE HUMAN FACTORS IN SPACE FLIGHT. By James S. Hanrahan and David Bushnell. New York, Basic Books Inc., 1960. 263 pp. $6.00.

Space Biology reviews the experiments in space travel and its hazards to living things from da Vinci's Alpine expedition of 1590 to Project Mercury. The two writers are not biologists (one an expert in Latin American history, the other an historian of science, both now historians at the Air Force Missile Development Center) and it is possible the book derives its easy comprehensibility and smooth integration of hundreds of experiments and papers to their prior training. The layman has seldom been offered a work

which so comprehensively sketches out the problems of space travel and the most recent investigations. Russian as well as American results from telemetering artificial satellites are included and their value interpreted. The individual with competence in non-space biology will discover a useful and stimulating summary of research with references to papers which will carry him farther into intricacies than the authors choose to travel.

One notes the dependency of early American space and aero-medical research upon the cadre of German scientists such as the Haber brothers, Gauer, Gerathewohl, and especially Hubertus Strughold. Also evident, although not stressed, is the damage done to our biological conquest of space by sudden and determined budget cut-backs prior to Sputnik. An austerity drive during the summer of 1957 stopped flights at the Holloman Aeromedical Field Laboratory investigating subgravity effects upon humans. The authors state, "this was one of the many examples of the difficulty of getting and keeping support for basic scientific research in our space program." From 1953 to 1957 only the Russians were working in the field of animal rockets.

Three major problems in space travel are considered: the space vehicle, g-forces and weightlessness, and the radiation hazards. The historical aspects of each topic is discussed so that the non-expert can follow the esoteric paths from where they first branch from our common experience. Although written with a rather bland style, the book reads quickly and interestingly and will be of great service to the citizens who would like to see pieced together, against a background of professional literature, the scattered reports of flight from the earth.

DAVID F. MUSTO

HYPOTHERMIA. By A. Cecil Taylor (and others). Annals of the New York Academy of Sciences, vol. 80, art. 2, pp. 285-550. New York, 1959. $3.50.

The New York Academy of Sciences has devoted an entire issue to a review of the current concepts of hypothermia. To the student of hypothermia, it is the most authoritative reference text on the subject and, therefore, is entitled to enthusiastic acceptance. This work can be regarded as a sequel to the first collective effort published in 1955 by the National Research Council entitled *The Physiology of Hypothermia.* The authorship and fundamental approach are almost identical. The information is related to the basic physiologic and biochemical changes that occur in hypothermia and much of it is presented in highly technical terms.

Five chapters are devoted to functional changes in the heart. The threat of ventricular fibrillation is the most serious limitation on the clinical use of hypothermia. Whereas the cause of this arrhythmia remains unknown, the available information on possible mechanisms and the pharmacologic control are discussed.

Hypothermia alters every measurable phenomenon of gas transfer and an awareness of these changes is essential to an understanding of the cooled state. The effects of temperature on pulmonary function are discussed in detail with monograms included for calculation of serum pK, pH and PO_2.

The hemodynamic and metabolic change observed in the hypothermic liver have been measured. Although much remains unexplored, the non-uniform depression of the many functions is made clear and the protection against anoxia that hypothermia offers the liver is described.

Renal physiology lends itself well to accurate measurement and advantage is taken of this to investigate the degree of depression of renal blood flow, glomerular filtration rate, etc., at moderate levels of hypothermia. The urine volume is known to remain constant during hypothermia and the mechanism for this is described. This chapter will be especially rewarding since the terms and diagrams will be within the grasp of all on first reading.

In four chapters the central nervous system is considered. This is an area in which extensive clinical experience with hypothermia has been gained. The several authors have described the response of the normal brain to hypothermia and the central nervous system control of body temperature. Also described is the value of hypothermia in preventing the progression of thermal and anoxic injuries in the brain even when there has been a delay of 3-4 hours.

In profound hypothermia the temperature is reduced below 15°C and the heart is in arrest. Under these conditions operative procedures can be undertaken that are not possible at normal temperatures or in moderate hypothermia. It requires little imagination to grasp the potential value of this modality.

Because this review serves such a useful purpose, it is hoped that a comprehensive report at regular intervals will be continued.

GEORGE F. GOWEN

BONE AS A TISSUE. Kaare Rodahl, Jesse T. Nicholson, Ernest M. Brown, Jr., Eds., New York, McGraw-Hill Book Co., Inc., 1960. 358 pp. $16.00.

This book is an excellent review of some of the current research and clinical advances made on the skeletal system. The subject is so vast and complex that it could not possibly be covered completely in any single volume, and this work makes no such attempt. The subjects covered include osteoporosis, dynamics of calcium metabolism, ultrastructure of bone, vitamin D, parathyroids, citric acid, calcium, and phosphorous, as they relate to bone. While most of the material has been published by the various contributors elsewhere, at the present time there is no better collection of these subjects available. The various contributors to this volume presented the bulk of this material at a conference held at the Lankenau Hospital in Philadelphia in October 1959. The authors' qualifications in their particular fields are unexcelled.

It is inherent in any volume having multiple contributors that the reader will find differences of opinion and a lack of continuity. This book does not present a singular, comprehensive, or, in certain cases, the most widely held view of the subjects discussed. However, one wishing to familiarize himself with the current concepts of these subjects would profit from a careful study of this volume. The illustrations, bibliography, style, and form of the book are excellent.

W. O. SOUTHWICK

PHYSIOLOGY OF PREMATURITY. (Transactions of the Fourth Conference—March 1959.) Jonathan T. Lanman, Ed. Madison, New Jersey, Madison Printing Company, 1960. 187 pp., $4.50.

This is the fourth of a series of yearly conferences on the physiology of prematurity, which are attended by 25 invited persons of varied disciplines. These bring their different approaches to bear in the discussions which center about an informally presented topic on a given day in which one or two of the guests are featured. This conference was built around three topics: heat regulation (presented by Dr. S. Z. Levine and Dr. E. F. Adolph); hypothermia and asphyxia of the newborn (presented by Dr. James A. Miller, Jr.); and chemical structure, functional integration and renal regulation as factors in the physiology of the newborn (presented by Dr. Elsie M. Widdowson). As in the past, with but one outstanding example, the topics have been both timely and pressing (the one example of a topic that "never should have been" was in the third (1958) conference in which a presentation of experience with glucuronic acid in treatment of bilirubinemia was presented). Each topic in the present conference was well presented and explored by the featured speakers as usual. Furthermore, this reviewer was almost equally excited by each presentation, so that it would be difficult to pick any one as more stellar than another.

Dr. Frank Fremont-Smith introduces this conference with a defense of the format. He states that these "provide an opportunity for informal give and take among the participants" and comments also that "considerable interest and some criticism" has been aroused by the style of publication of "editorial permissiveness." It is our feeling that the adverse criticism toward these issues are justifiably directed not toward the free associations of the participants but toward the religious stenographic recording of these free associations which to the reader who has not attended the conference suggests that these conferences are carried out in a state of chaos and near-anarchy. Like its preceding conference one can ferret out the wealth of information and perspective to be found here only with diligent effort, by ignoring innumerable interruptions, and by maintaining a constant rigidity of purpose. One is seized with desire to snatch up a pencil and wield a heavy editorial hand and add some much needed paragraphs of summation as well.

Despite the above criticism which results in a less readable text, this is a valuable and desirable addition to anyone's library on the newborn and prematurely born infant.

LOUIS GLUCK

SOMATOSENSORY CHANGES AFTER PENETRATING BRAIN WOUNDS IN MAN. By Josephine Semmes, Sidney Weinstein, Lila Ghent and Hans-Lukas Teuber, Cambridge, Massachusetts, Harvard University Press, 1960, 91 pp. $4.00.

This unusual work is a presentation of a detailed analysis of permanent losses in somatosensory function following penetrating brain wounds in previously healthy young adults. This study, which has been carried on for over ten years, has mainly utilized a group of over 300 war veterans with combat

injuries of the nervous system. Therefore, this is mainly an analysis of the later after-effects of penetrating brain wounds. The book consists of about 56 pages of well-written succinct text and an extensive appendix with 20 detailed tables of results. There is a useful and thorough list of references and a well defined review of the problem of the cerebral contribution to somatic sensation.

The investigators have used as a control group, other veterans without penetrating brain wounds. Three major tests of somatic sensation were applied: punctate pressure sensitivity, two-point discrimination, and point localization, as well as a test of the ability to perceive the direction of small passive movements of the distal phalanx of the middle finger. It has been assumed generally that the representation of sensation of the left hand in the right hemisphere is the mirror image of that of the right hand in the left hemisphere. The results of this investigation produced unexpected data which cast doubt on the validity of this assumption, and suggested instead, that the mode of organization of sensation in the brain is not the same for the right and left hands. Cases with impaired sensation of the right hand showed the classical localization of lesions in the left cerebral hemisphere. Cases with impairment of discriminatory perception in the left hand had cerebral lesions which were widely dispersed. The sensory abilities of the left hand appear, from this study, to be more diffusely represented in the contralateral hemisphere than that of the right hand. Previous studies of cerebral sensory functions have indicated that the left and right parietal lobes are not functionally equivalent, but these differences were mainly in the sphere of complex perceptual disturbances such as the dysphasias, agnosias, apraxias, and anomalies of spatial orientation. The differences described by these workers did not appear to be related to these more complex disorders of sensory function, nor to the presence of a seizure disorder.

This monograph is a model of well presented and analyzed neuropsychological data. The results are intriguing and thought provoking since they lead to important questions concerning the differential organization of the two cerebral hemispheres.

GILBERT H. GLASER

VIRUS GROWTH AND VARIATION. The Ninth Symposium of the Society for General Microbiology. A. Isaacs and B. W. Lacey, Eds. Cambridge, Cambridge University Press, 1959, 272 pp., $7.00.

The publication of symposia on virology has supplanted publication of integrated texts and monographs to a large extent in recent years. This trend has been fostered by the increasing pace of research and the brevity of the period before a book becomes out of date. Symposia, however, often have serious flaws when put into printed form. A paper, prepared for one of these oral presentations, is prepared with the immediate audience in mind. Often it is directed chiefly toward those few in the original audience who are already sufficiently familiar with the subject to participate in discussion from the floor. Hence these papers tend to concentrate on data that are new at the time of the presentation and to take for granted a knowledge of

pertinent background information. Since new data are usually available to the author only from his own laboratory, work of others is rarely covered adequately. In the course of publication the novelty of the studies reported in a symposium is inevitably lost, the give and take of the discussion is seldom reproduced and one is left with a disconnected group of papers, each emphasizing work in one laboratory, work that, by this time, has appeared in more complete form in the regular scientific journals.

These general limitations on published symposia apply to the symposium of *Virus Growth and Variation* as well as to other such collections. Nevertheless, taken individually, several of the papers in this symposium will be of interest to a wider audience. The two papers on microscopy and electron microscopy might be mentioned in the latter respect. The use of acridine orange to identify ribo-nucleic acid and desoxyribonucleic acid is described here by Anderson, Armstrong and Niven in more detail than has been available heretofore. A well-reproduced color plate gives some idea of the striking results that may be obtained. Morgan and Rose have added another series of electron micrographs to their extraordinary studies on adenovirus and influenza. Here we may see crystals with their component parts resolved into row on row of particles and the virus particles agglutinating cells by the formation of myriad bridges. A review by Isaacs of recent work in interferon is welcome. This unusual substance, produced by cells in response to virus infection, is capable of suppressing growth of many viruses in addition to suppressing the growth of the virus which elicits its own production. While it is probably vain to hope that this substance may prove to be to viruses what antibodies are to bacteria, study of the system may lead the way to this long sought goal.

Probably the number of persons who will want to read this book in its entirety will be limited. Many others, however, might find specific points of interest to themselves by glancing over the chapters and pausing where their eyes catch a particular point.

FRANCIS L. BLACK

PRINCIPLES OF ANIMAL VIROLOGY, 2d Edition. By F. M. Burnet, New York, Academic Press, 1960, 490 pp. $12.00.

Sir MacFarlane Burnet, who has recently received the Nobel prize for his work on immune tolerance, has probably been better known for his studies in virology. The first edition of his book *Principles of Animal Virology* was enthusiastically reviewed in volume 28 of the *Yale Journal of Biology and Medicine*. The present edition retains the assets that made the first such a success. It is easily readable because it is not simply a compendium of facts but a well-integrated whole. The many facts contained in the book are related one to another and used as the basis of various theories and carefully qualified generalizations which tend to give meaning and cohesion to each chapter. Doubtless, many of Dr. Burnet's hypotheses will prove erroneous but all of them are worth careful consideration and they often serve to suggest new experimental approaches to old problems. Parenthetically, it may be mentioned that Dr. Burnet's chief contribution to the study of immune tolerance consisted of formulating the basic theory which

was later verified principally by others. One may note his theories of the relationship of viruses to cancer as an example: Viruses may cause cancer by making cells unresponsive to normal control mechanisms, or possibly, by transducing abnormal genes from one cell to another or, perhaps, the so-called cancer viruses may actually be abnormal genetic material derived from the first host.

The preface to the second edition is dated November 1959 but in the text mention is made of the revision of some portions having been completed in 1958. References to studies published through 1958 are reasonably complete but 1959 references are largely confined to Australian work. Such a delay seems moderate in view of the time required for transit of journals to and from Australia. In addition to the new material in this edition, a certain amount of judicious pruning has been carried out to remove some material that was of limited importance.

Like the first edition, the second is a stimulating and valuable book, yet it has fallen somewhat short of the high standard that had been set. Every chapter has been revised but the revisions tend to be superficial and occasionally incomplete. For instance, the revolutionary studies on infectious nucleic acids are only alloted one page and the unusual association of varicella virus with its host cell in tissue culture is not mentioned. The early retrospective data on congenital defects due to rubella are retained and the more recent prospective studies, which have indicated much lower incidences of abnormalities, are not mentioned. Perhaps the reason new developments have been awarded so little consideration lies in the author's attitude as expressed in the preface: "We had passed the last golden age of virology by 1959 . . . a new orthodoxy is established." Whether or not this attitude is correct, it is hardly compatible with much enthusiasm for new developments. There are few virologists who would be willing to dismiss the new field of infectious nucleic acids, the extensive new data on tumor viruses of mice and the hundreds of newly identified viruses as part of an established orthodoxy.

These reservations on the present edition must be kept in proper perspective. They are criticism made on comparison of the second edition with the first. This book has no peer in its field for coherent readability and may be recommended both to scientists wanting to learn the basis of animal virology and to specialists seeking renewed inspiration.

FRANCIS L. BLACK

CELLULAR ASPECTS OF IMMUNITY. G. E. W. Wolstenholme and C. M. O'Connor, Eds., Boston, Little, Brown and Co., 1960; 495 pp., $10.50.

This symposium was held in the Abbey of Royaumont, just north of Paris, in June 1959. As with most of the conferences sponsored by the Ciba Foundation, a small selected group of 32 investigators, presently most active in this particular field, participated in a three-day discussion on antibody synthesis. As noted by the Chairman, the emphasis shifted from a study of antibodies *per se* to a study of the immunologically competent cell.

This volume is not intended for those desiring a brief survey of the available knowledge on antibody synthesis. Many of the articles require the

reader to have a fairly extensive knowledge of protein chemistry, immunology, and genetics. However, a real attempt is made to cover the broad field in a fairly systematic fashion. The beginning chapters discuss the nomenclature and ultrastructure of plasma cells and their precursors as well as the routes whereby antigen is incorporated into the cell. The latter chapters are concerned with the action of antibodies on living tissues with particular reference to anaphylactic reactions, homograft reactions, and antigen antibody complexes resulting from autoimmunization.

One of the most excellent chapters is a panel discussion on the clonal selection theory of antibody formation. This hypothesis proposed by Burnet, based on the ideas of Jerne and Talmadge, supported by the work of Nossal, and championed by Lederberg has become a major controversial theory and an impetus to multiple new experiments. It simply proposes that in any population of mesenchymal cells there is a certain number of different clones, each composed of cells immunologically competent towards a certain antigenic determinant. A particular antigen, if incorporated, stimulates further proliferation of the clonal cells, which are ultimately converted into antibody producing plasma cells. Although initially, it was postulated that each clone could only produce one antibody, later work by Lennox and Cohn with phage antigens proved that each cell could produce at least two antibodies and the original theory will probably undergo further modification.

The book in general deserves an excellent endorsement and will simulate considerable interest in many peripheral fields.

DONALD W. KING

PRINCIPLES OF HUMAN GENETICS, 2d Edition. By Curt Stern, San Francisco, W. H. Freeman & Co., 1960. 753 pp., 265 illus., 124 tables. $9.50.

This is the second edition of a textbook which in its first edition received a good deal of critical acclaim since it appeared in 1949. During the past decade human genetics, a relatively new field, has undergone many fundamental changes and has become progressively of greater importance. This new book accurately reflects these changes by its increased length (150 pages and 65 illustrations more than the previous edition), including many new and revised chapters. As Stern mentions in his introduction, there have been a number of important lines of advance, e.g.:

1. Recognition of the true number of man's chromosomes and advances in cytogenetics.

2. Discovery that certain pedigrees for special traits were untenable.

3. Elucidation of the role of the Y chromosome in sex determination.

4. Improvement of biochemical knowledge of the inborn errors of metabolism such as galactosemia and alkaptonuria.

5. Recognition of the universal existence of polymorphism (i.e., the presence of many alternative alleles in fixed ratios, such as A, B, O blood alleles) and attempts to explain this phenomenon.

6. Expansion of knowledge of the relationship between disease and blood groups and hemoglobin constitution, exemplified by advances in research on Rh and sickle cell anemia.

7. Most significantly, perhaps, the increased awareness of the profound effects of x-rays and other radiation on mutation rates.

All of these new discoveries receive greater attention in this edition. For example, the definitive proof that it is the presence of a Y chromosome and not the absence of an X which determines a male in humans has permitted a sound discussion of intersexual deviations. Cytogenetic techniques have become so refined recently that the precise normal complement of chromosomes is now known and states such as Mongolism have been explained in this light. The review of radiation hazards has evolved from a section of the chapter on the significance of mutations to a full chapter in itself. Stern states the dangers of radiation with obvious concern for the future of mankind, but with genetic precision, pointing out the assumptions implicit in the grim estimates of tragedy he presents and listing the uncertainties involved. He certainly cannot be accused of overstatement with intent to frighten. Yet the genetic evidence he cites supporting the often-repeated warning of the dangers of nuclear testing gives that warning a renewed impact which cannot fail to frighten anyone but the most callous reader.

This book, as the title states, is designed primarily to present principles, and succeeds admirably in doing so for an extremely wide range of subjects. The paucity of textbooks of human genetics before 1949 was due to the lack of fundamental knowledge of human mechanisms, so that genetic principles were best taught in a course on general genetics, with man "as an appendix to other experimental organisms," to quote from the preface to the first edition. Elementary "standard" considerations like meiosis, probability, mutations, and Mendelian single-factor inheritance now can be covered using *human* examples. Problems of consanguinity, sex ratios and sex determination, multiple alleles and blood groups, a bit more advanced from the elementary, are also considered, and to complete the spectrum there are chapters on medicolegal genetics, problems of genetic counselling, radiation hazards, heredity and environment (now including an enlarged section on the genetics of pathological conditions) and the origins of human diversity. These latter topics are within the province of anthropology and psychology, but definitely show a geneticist's approach.

Stern has acquired greater facility in his use of English, an adopted tongue, and even in chapters where the content has remained virtually the same there has been some rephrasing in the interest of greater clarity. As in many basic textbooks, there are didactic questions at the end of each chapter, but these are in the main stimulating, and fortunately the body of the chapter is devoid of the pedantic tone which so often accompanies such questions. Stern illuminates but never oversimplifies, even at the risk of leaving a subject unsatisfying and equivocal (cf. the chapter on sex ratios). It is a credit to his approach that solutions are not provided for all the problems posed.

In short then, this is a book of considerable value, most obviously to psychologists, obstetricians, pediatricians and others who may be called upon to counsel prospective parents, but the enormous range of disorders influenced by the genetic constitution of the host makes it imperative that this book be read as a text in *basic* medical science. It is encouraging to know that a comprehensive survey of human genetics such as this exists, and it is to be hoped that this neglected field will receive more attention, perhaps as a direct consequence of its presence.

M. S. M.

AN INTRODUCTION TO RADIATION COUNTERS AND DETECTORS. By C. C. H. Washtell. Philosophical Library, New York, 1960, 115 pp. $6.00.

The larger part of this book is devoted to brief descriptions of Geiger counter tubes, photomultipliers, and phosphors, and to lists of counting equipment taken from the catalogues of certain manufacturers in England. There is also an introduction to radioactivity and its measurement, but this is of little value because of the author's manner of presenting this material. The following sentences illustrate this vague and rambling style of writing. Discussing artificial radioactivity he writes, "At the turn of the nineteenth century, Thomson and his followers began to break up the atom and to postulate theories regarding its constituents based upon experimental work which showed that the mass of an electrified body could be changed by setting it in motion; the faster it moved the greater its mass became in defiance of the 'unalterable-mass' concept." And then again, under the heading radioactive decay he says "Since we know that the emanations from a radioactive element are caused by particle disintegration and quanta radiation, and that the decay in activity which occurs causes a reduction in the life of the element as a radioactive substance, the rate of this decay provides a further characteristic by which it may be identified." There is a short list of some of the characteristics of a number of radioactive isotopes available for experimental work. Tritium and the iron isotopes could have been included in this because of their usefulness. The author is more at home where he is describing equipment that he has seen and handled, but the book is of very limited usefulness even as an introductory manual. Unfortunately it can not be recommended.

PAUL HOWARD-FLANDERS

QUANTITATIVE PAPER CHROMOTOGRAPHY OF STEROIDS. D. Abelson and R. V. Brooks, Eds., London, Cambridge University Press, 1960, 103 pp. $6.00.

This volume represents the edited proceedings of a Conference on Quantitative Paper Chromatography of Steroids held in London at the Ciba Foundation on 1 July 1958. The conference was undertaken under the auspices of the Society for Endocrinology, and the edited proceedings are presented as the eighth in a series of Memoirs of the Society.

The scientific caliber of the conference may best be illustrated by the roster of the eighteen distinguished participants: D. Abelson, R. V. Brooks,

I. E. Bush, C. L. Cope, A. Gowenlock, N. J. Holness, V. H. James, A. E. Kellie, C. J. O. R. Morris, R. Neher, E. C. Osborn, R. V. Short, E. R. Smith, M. Stack-Dunne, J. F. Tait, S. A. S. Tait, M. Vogt and I. D. P. Wootton. Through the co-ordinated efforts of these scientists, the proceedings present a timely exposition of the current status of steroid chromatography on filter paper.

Detailed consideration is given to refinements of paper chromatographic methods, in an effort to increase the resolution of steroid fractionations. Modifications of the Zimmermann reaction and the tetrazolium reaction are presented which facilitate measurements of 17-ketosteroids and reducing steroids on paper chromatograms. Especial attention is devoted to quantitative estimation of steroids by measurement of soda fluorescence.

Dr. Abelson and Dr. Brooks merit congratulations upon their editorial skills which have captured successfully the lucid discussions which enlivened the conference. These edited proceedings should prove of practical value to biochemists and clinical scientists who are engaged in the application of chromatographic technics to steroid fractionation.

F. WILLIAM SUNDERMAN, JR.

WHAT PRICE MEDICAL CARE? A Preventive Prescription for Private Medicine. By Sir Eagle Page. Philadelphia, W. B. Lippincott, 1960, 160 pp., $3.50.

"Medicine in the United States needs help. It needs help, and needs it now, because ordinary and conventional approaches to the financing problem of people needing medical and hospital care will no longer meet an urgent public need." The above, quoted from the introduction, was written by an executive of one of the Blue Cross plans; this statement will be accepted by most persons who are familiar with the current medical care situation in our society. Sir Earle Page, the author of the Australian Medical Plan, has been induced, by friends in this country, to write a "prescription" which will help medicine in the United States to meet its challenge.

The author, a surgeon and politician, is no doubt familiar with the several aspects of this problem as well as the solutions which have been tried in other countries; however, his "prescription" is limited to an anecdotal discussion of his health plan, tales of the practice of surgery in the early twentieth century, and pleas for the preservation of the intimate doctor-patient relationships.

The Australian Plan is described as, " . . . a system that is the product of complete cooperation among all the parties involved, which are the public, the medical profession, the insurance societies, and the government." The author notes the many similarities between Australia and the United States; however, he does not give adequate emphasis to those major differences which would greatly obstruct the application of his plan to our society. He comments that, "government has virtually been left out as a partner in the United States" but overlooks the strong opposition of organized medicine to the government's taking a role in medical care. Nor does he mention the confused variability and structure of current voluntary health

insurance in this country. True, we have a great quantity of voluntary health insurance, but quantity and effectiveness are not synonymous.

By dichotomizing the challenge and allowing only the alternative of sound medical practice, which preserves the physician-patient relationship, or socialism, Dr. Page permits himself to conclude that, " . . . the only practicable scheme that will relieve people from the haunting fear of hospital and medical expenses is a system based on voluntary insurance, backed by government aid."

Our first need is for cooperation among interested parties in the organization and development of the philosophy and effectiveness of voluntary health insurance. The accomplishment of this prerequisite could validate the author's conclusions.

What Price Medical Care offers the reminiscences of an octogenarian who has witnessed much change in the complex of medical care; however, the question remains unanswered while the challenge continues to grow.

WILLIAM L. KISSICK

NOTES OF A SOVIET DOCTOR. By G. S. Pondoev. New York, Consultants Bureau, 1959. 238 pp. $4.95.

Notes of a Soviet Doctor is a translation of the second edition of a book accepted as the handbook of Soviet medical ethics. As such it should be read to ascertain the purposes and methods of the Soviet Communist Party, as they relate to medicine, rather than the political coloration and sincerity of the author, and, by extrapolation, the Soviet intellectual in general.

The more obvious purpose is to define medical conduct, especially in regard to the doctor-patient relationship, for medical students and recent graduates, the majority of whom have gone into rural practice without internship training or the equivalent. As Dr. Pondoev puts it, "We older doctors learned our science under different conditions of life; at the end of our course many of us were able to work for a year or so in a hospital under the guidance of older colleagues. Nowadays the young doctor finds himself in a very different situation; . . . although his theoretical training is adequate, . . . he lacks confidence in his approach to the patient . . . because it is difficult to pass on such knowledge theoretically, . . . and requires a longer time than is available in the medical curriculum."

Another purpose is to create an historical and ideological perspective on Russian medicine. Heroes of western medicine are belittled and their accomplishments criticized on the basis of their incorrect ideological outlook. We are urged to "take all that is useful to us from medical antiquity and examine it in the light of materialistic doctrine." In that light, Claude Bernard is criticized because he "entirely ignored the disturbance in the external natural environment of the organism, not to mention the social environment as well." The ideological helplessness that Hippocrates introduced by thinking of medicine as an art was set right, "to the honor of the Russian medical school of the nineteenth century, by the great founders of Russian clinical medicine, S. P. Botkin and A. A. Ostromov."

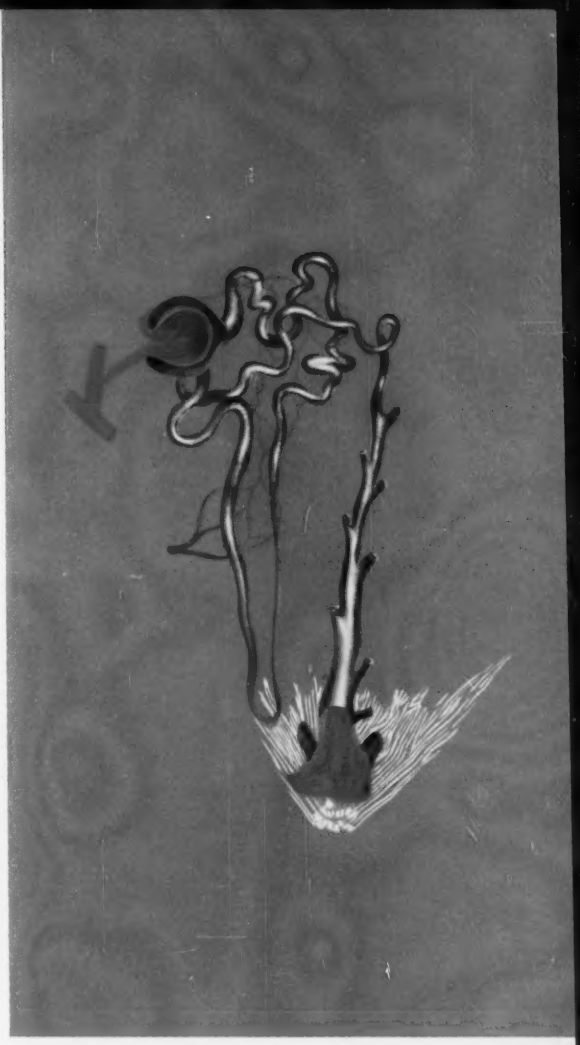
This book is also written to encourage young people to choose medicine as a vocation. Dr. Pondoev is personally evangelical about the intense satisfaction accompanying the prevention and treatment of disease; the approbation of the government and the Communist Party are evinced in a subtler manner. "Science exists for the service of man, and in a socialist state there can be no science which does not serve practical purposes, no science for science's sake." Medicine, the science *par excellence* applied to man, is regarded as the culmination of the Marxist theory of science. Dr. Pondoev continues, "The doctor is thus a member, with a specialized medical education, of a large and complex system, the purpose of which is to protect the health of the community." The doctor is thus the patriotic soldier of science; a career in medicine as the fusion of vocation, nationalism, and ideological correctness becomes clearer in this quote: "Only that doctor who combines a specialist's knowledge of medicine with a Marxist and Leninist interpretation of society and who is firmly grounded in the materialist doctrine . . . can be successful in his work and can fulfill his high vocation to the honor of his country."

That Pondoev, himself, is not in rigorous agreement with the implications of a planned socialist service is evident from his recollections of the "'free profession'" of the past, and his evocation on several occasions of the innate duty of the physician. That not all the members of his profession are wholehearted supporters becomes evident later as the Honored Physician is forced to admit, "A case of successful treatment of a patient by the doctor is not merely an act of humanitarian behavior by the doctor to an individual patient, but at the same time it restores the strength of the group. [That] there are doctors who have not yet succeeded in developing a group sense within themselves . . . must be regarded as a gross infringement of socialist morals and it must be rigorously stamped out from the medical profession."

Pondoev is not content to demonstrate the adequacy of Soviet medicine, but feels compelled to degrade and debunk the western physician who was not "rescued from the pernicious influence of a bourgeois ideology and inspired with high moral, social, political, and cultural principles. . . ."

This book does indeed concern itself with medical ethics and with the doctor-patient relationship in a largely uneducated population, but its primary interest is as a policy statement of the Soviet system. It throws an interesting light on the development of a system of medical care in a totalitarian country.

J. F. B. H.



on the pathogenesis of pyelonephritis:

"An inflammatory reaction here [renal papillae] may produce sudden rapid impairment of renal function. One duct of Bellini probably drains more than 5000 nephrons. It is easy to see why a small abscess or edema in this area may occlude a portion of the papilla or the collecting ducts and may produce a functional impairment far in excess of that encountered in much larger lesions in the cortex."[1]

The "exquisite sensitivity"[2] of the medulla to infection (as compared with the cortex), highlights the importance of obstruction to the urine flow in the pathogenesis of pyelonephritis. "There is good cause to support the belief that many, perhaps most, cases of human pyelonephritis are the result of infection which reaches the kidney from the lower urinary tract."[3]

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References: 1. Schreiner, G. E.: A.M.A. Arch. Int. M. **102**:32, 1958. 2. Freedman, L. R., and Beeson, P. B.: Yale J. Biol. & Med. **30**:406, 1958. 3. Rocha, H., et al.: Yale J. Biol. & Med. **30**:341, 1958.

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